THE
BRITISH JOURNAL OF SURGERY

VOL. XXIII JULY, 1935 No. 89

IPSISSIMA VERBA

BY SIR D'ARCY POWER, K.B.E., LONDON

VI. TREVES' FIRST APPENDIX OPERATION

INFLAMMATION of the vermiform appendix and the possibility of surgical interference for its relief was beginning to attract attention in England in 1885 and in Melbourne some three years earlier. The condition was still known as 'typhlitis', 'perityphlitis', and 'idiopathic peritonitis', but no formal operation was undertaken for its cure. The abscess was sometimes opened when the patient had been fortunate enough to survive the suppuration and the measures taken to cure it. The case reported by Mr. Frederick Treves appears to have been the first in this country which was undertaken deliberately for the cure of a chronic and relapsing inflammation, though he did not remove the appendix.

Mr. Charters J. Symonds[1] removed an appendix successfully at Guy's Hospital on Aug. 24, 1883. The patient suffered from recurrent typhlitis associated with a 'calculus', but, in reporting the case afterwards, he said that he had seen 23 fatal cases of typhlitis, but "thought that surgeons would long be deterred from opening the abdomen and removing the appendix although such a proceeding might lead to recovery in otherwise hopeless cases".

Mr. J. H. Webb,[2] of Melbourne, gave bolder advice a year later and came very near to anticipating Treves as a pioneer in the deliberate removal of the appendix. He wrote that "three cases of perforation of the Vermiform Appendix have occurred in my private practice during the last five years. All have died and such lesions seem to be commoner than is generally supposed. Drugs are useless but patients should not be left to die. The mind once made up immediate action should be taken. I would certainly advise abdominal section and if I ever have another case go through my hands I shall open the abdomen, say Nay, who will. The operation will at least give a chance." It does not appear that Mr. Webb ever had the chance, for nothing more is heard of him.

The case reported by Mr. Treves[3] is in the following words. He was then aged 34 and was full Surgeon at the London Hospital:—

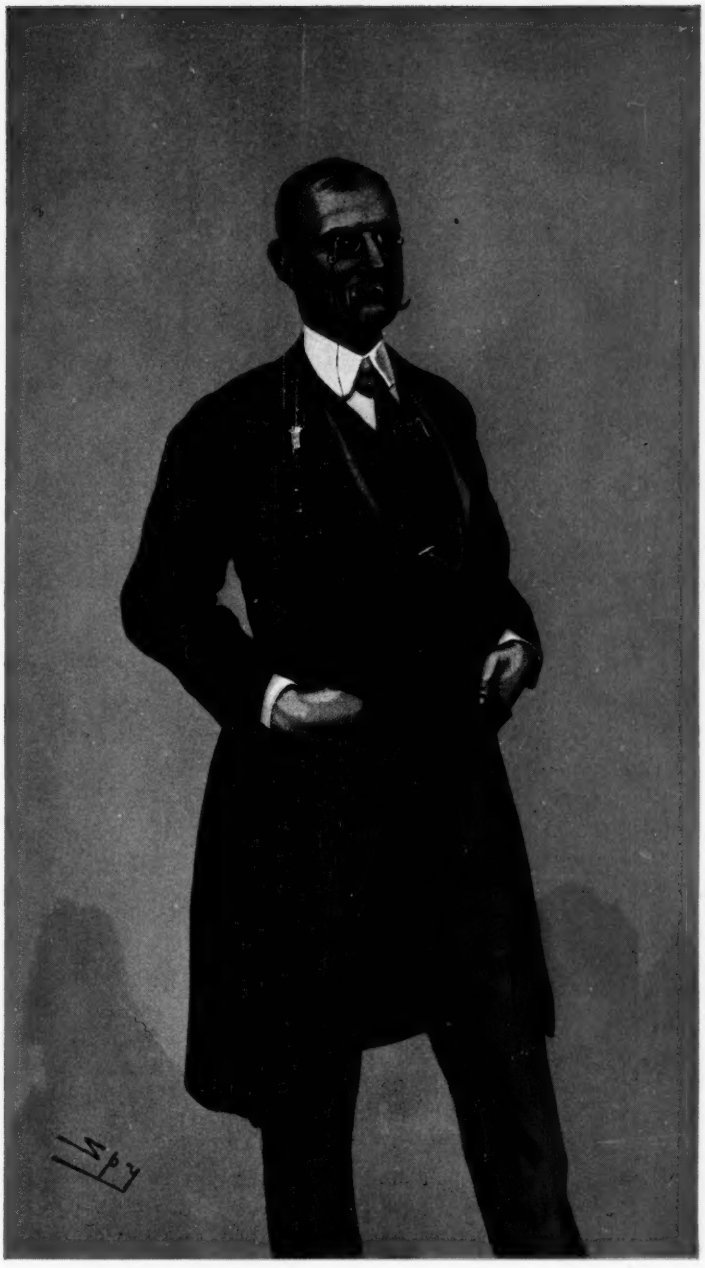
"The following case afforded the only opportunity I have had of carrying this proposed treatment into practice. The case was simple and the patient made a sound recovery.

"A man, aged 34, a working engineer, was admitted into the London Hospital

under the care of Dr. Stephen Mackenzie, on December 31st, 1886, suffering from typhlitis. He had been a healthy, vigorous man of sober habits. He had had no illness except an attack of bronchitis fifteen years ago. He had been free from abdominal trouble previous to the present affection and his bowels had always been regular. Early in August, 1886, he was seized with pain in the right iliac fossa, followed by local swelling, vomiting, and constipation. This was his first attack of typhlitis. He was confined to bed and for a while improved under treatment, but after a week or so of freedom from pain, the symptoms reappeared with renewed vigour, the swelling and tenderness in the iliac fossa became once more pronouced, and the patient, to use his own expression ' was as bad as ever again '. Between the attacks he was not well enough to leave his bed, nor was he ever quite free from a sense of discomfort in the cæcal region. He was confined to bed for three months, i.e., from the commencement of August to the end of October. In November he was able to resume his work, and for a while did not complain of any trouble in his abdomen. He found, however, that his bowels did not act so freely after his illness as before. He remained well until December 27th—four days before his admission into the hospital—when he was once more seized with pain in the right iliac region attended by local swelling, sickness, and much prostration. He at once took to bed, but as his symptoms did not abate he came to the hospital.

" When admitted he presented the ordinary symptoms of typhlitis. He was well nourished and exhibited no organic disease other than that in the abdomen. A globular swelling occupied the right iliac fossa and was the seat of extreme tenderness. The abdomen was but slightly distended, the bowels were confined, but there was no vomiting. His temperature was 99·2° F. Opium was given and the constipation was relieved by enemata. His progress was very slow, the pain in the abdomen persisted, the swelling remained tender and diminished but sluggishly. It was not until February 8th, some six weeks after the commencement of the attack, that the abdominal symptoms had entirely disappeared. The patient was much weakened by his confinement in bed, but he did not complain of pain or tenderness in his abdomen, and no trace of any iliac swelling was left. Dr. Mackenzie now requested me to see the patient with reference to possible operative interference. Dr. Mackenzie was of opinion that the patient would be the subject of further attacks, and endorsed the suggestion that the abdomen should be opened and the cæcal region explored in the hope that the cause of the trouble might be removed.

" I performed laparotomy on February 16th [1887]. I opened the abdomen by a vertical incision immediately over the region of the cæcum. That part of the bowel was soon exposed. It was free from adhesions. There were evidences of old peritonitis about the appendix. To the base of that process the omentum had become adherent. The mesentery of the appendix was shrunken and had bent the tube upon itself at an acute angle. The part of the process on the proximal side of the bend was of normal aspect, that on the distal side was distended, was greatly thickened, and formed a rounded swelling the size of the end of the forefinger. I had intended to remove the appendix, but it at once became straight on cutting away the omentum. I bared the convex side of the tube of peritoneum, thinking that fresh adhesions might occur upon that side and so hold the appendix in a straight position. The whole process only measured two inches and a half.



FREDERICK TREVES

UNIV. OF MICH.

I set free the omentum, sutured a small rent in the peritoneum that had been made during the examination, and closed the abdominal wound. It was evident that the shrinkage of the appendix mesentery had so bent that tube as to occlude it. Mucus had accumulated beyond the bend, and becoming retained had excited the peritonitis. The lumen had not become obliterated and the end of the diverticulum had apparently not been perforated.

" The patient recovered without a bad symptom. On March 18th, some little time after he was up and about, he had some slight pain in the seat of the old trouble. It was apparently due to constipation, as it disappeared at once on the administration of an aperient. The patient was kept in the hospital for another month, in order to be under observation. He remained perfectly well and has since that time had no further abdominal trouble.

" In the majority of cases it would probably be wiser to remove the appendix. If this is done as much care must be taken to close the divided end of the tube as would be taken to close a hole in the small intestine. A mere ligature would not be safe. Two sutures would suffice to bring the mucous membrane together, and the peritoneum should then be adjusted over this line of union by several points of Lembert's suture.

" It must be remembered that peritoneal adhesions or a peritoneum scarred by adhesions will not possess the same plastic power as the normal membrane.

" In the event of the process being so greatly thickened that suture of its serous coat is impossible I should be disposed to fix the stump to the nearest point on the surrounding parietal peritoneum."

The meeting at which the paper was read seems to have been well-attended, and in the subsequent discussion the President—Mr. Timothy Holmes, of St. George's—said that many years previously he had operated unsuccessfully on a somewhat similar case. Mr. Marsh and Mr. Walsham, of St. Bartholomew's, had been equally unsuccessful. Mr. Hulke, of the Middlesex Hospital, was in favour of operation but did not mention any case where he had done it. Dr. Hare preferred leeching; Dr. Dickinson was wholly against operation, and Dr. Douglas Powell merely said that he thought the old term ' perityphlitis ' was better than ' inflammation of the vermiform appendix '.

REFERENCES

[1] SYMONDS, CHARTERS J., *Trans. Clin. Soc.*, 1885, xviii, 285.
[2] WEBB, J. H., " Notes on Three Cases of Perforation of the Vermiform Appendix ", *Melbourne Med. Jour.*, 1884, N.S. vi, 436.
[3] TREVES, FREDERICK, " Relapsing Typhilitis Treated by Operation ", *Med.-Chir. Trans.*, 1888, lxxi, 165, and *Proc. Med.-Chir. Soc.*, 1888, N.S. ii, 336.

CARCINOMA OF THE GALL-BLADDER*

By C. F. W. ILLINGWORTH
SENIOR ASSISTANT SURGEON, EDINBURGH WESTERN HOSPITAL

It is now well recognized that carcinoma of the gall-bladder is of quite frequent occurrence, but although numerous case reports and papers have appeared in the American and Continental literature, the subject has attracted little attention in this country. Its surgical importance, as a grave and generally fatal sequel to calculous cholecystitis, requires no emphasis.

During the last five years the writer has had the opportunity of making a close study of 30 cases, in the Edinburgh Royal Infirmary and the Western Hospital, and in addition has been given access to brief records of 20 other cases. Nearly all the cases have been under the care of Professor D. P. D. Wilkie, to whom the writer is deeply indebted for permission to put them on record.

HISTORICAL

The earliest reference to carcinoma of the gall-bladder appears to have been made by Maximilian Stoll, Professor of the Practice of Medicine in Vienna. In his *Ratio Medendi*, published in 1777, Stoll describes the post-mortem findings in three cases, all of which may reasonably be regarded as true examples of the disease under discussion, although later writers, following Courvoisier, have accepted only two.

Stoll's cases are described briefly, but succinctly. The first (" periit in ictero nigro ex scirrho sphincteris vesiculæ felleæ ") is remarkable in having arisen in a left-sided gall-bladder with complete transposition of the viscera. In the second case, an old woman who suffered from chronic jaundice, the gall-bladder was " simul scirrhosa, callosa et cartilaginosa ". Gall-stones were present in this case, the liver was " ulcerated ", and the mesentery also was scirrhous. In Stoll's third case also the nature of the disease seems reasonably certain, for he records " periit in ictero chronico nigro: in exenteratione inveni hepar, collum vesiculæ felleæ, mesenterium et receptaculum chyli scirrhosum ", and further evidence that the carcinoma originated in the gall-bladder is suggested by the final note, " bilis loco in vesiculæ fuit sanguis nigerrimus ".

Eighteenth century writings contain only one other specific reference to carcinoma of the gall-bladder, by Hallé in 1786. Matthew Baillie's case, in which the coats of the gall-bladder, above a quarter of an inch thick, were " studded with tubercles of a considerable size and very firm ", may also perhaps be included.

Thereafter the subject attracted little attention until the latter part of the nineteenth century, when a number of valuable papers appeared. Frerichs in 1861,

---

* From the Department of Surgery, University of Edinburgh.

in his treatise on diseases of the liver, remarked on the relation of gall-stones to carcinoma of the gall-bladder, whilst Musser (1889), Courvoisier (1890), and Ames (1894) gave excellent accounts of the disease. Indeed, it may be said that practically all our present knowledge of carcinoma of the gall-bladder, except upon the detailed histology, is derived from these writers, and more recent observations have served only to confirm and elaborate their findings.

FREQUENCY AND DISTRIBUTION

Frequency.—Numerous records from autopsy departments and surgical clinics indicate that carcinoma of the gall-bladder is far from rare. Lentze in 1926 was able to collect 890 case records, nearly all derived from German sources, whilst at least an equal number is to be found in the American literature.

It is difficult to give an exact estimate of the true frequency of the disease, for many cases doubtless go unrecognized, and as a result the figures obtained from death certification are unreliable. Surgical statistics, being derived from selected groups of cases, probably give too high an impression of the frequency.

The most accurate estimate available is to be derived from the autopsy records of large general hospitals. In the post-mortem department of the Edinburgh Royal Infirmary during the last sixteen years there were 36 cases of carcinoma of the gall-bladder in a total of 8490 autopsies. During the same period the cases of malignant disease of all types and regions numbered 1275. Thus carcinoma of the gall-bladder accounted for 0·42 per cent of all autopsies and 2·8 per cent of all malignant disease.

Surgical experience shows that carcinoma is found in from 1 per cent to 2·5 per cent of all operations on the gall-bladder. Professor Wilkie informs me that in 1057 operations on the biliary tract he has encountered 34 cases of carcinoma of the gall-bladder, an incidence of 2·2 per cent. Deaver found 16 cases of carcinoma in 1000 operation cases; Smithies 23 in a similar total; whilst Judd and Gray, from the Mayo Clinic, have reported 212 cases from the large series of 22,365 operations on the biliary tract.

Sex Distribution.—All observers agree that a large proportion of cases occur in women. Fütterer in 1901 collected 264 cases from the literature, of which 204 affected women (77 per cent); and many later writers have reported a similar sex distribution. In the 50 cases reported in this paper there were 40 women, an incidence of 80 per cent.

Age Incidence.—Although there are records of carcinoma of the gall-bladder occurring at all ages from 22 to 95, the great majority fall into the age group 50 to 65 years, and the disease is distinctly rare before the age of 40 years.

In the present series the youngest patient was aged 39 years, the oldest 80 years. Thirty cases occurred between the ages of 50 and 65, and the average age was 60·6 years.

In the literature the youngest patient recorded is that of Proescher—an Italian male, aged 22, though in this case the diagnosis is not free from doubt. Shelley and Ross give references to three cases occurring at the age of 25 years, while there are a number of cases reported occurring between the ages of 28 and 30 years.

The literature contains numerous references to a case of Moxon's, which is stated to have occurred in a child aged 4 years, but reference to the original paper

shows that he has been misquoted. Moxon did not mention the age of his patient, but his description of the patient's intemperate habits and his occupation as a brushmaker effectively disposes of the suggestion of childhood.

ETIOLOGY

Certain factors that require to be discussed in the etiology of carcinoma of other organs may be mentioned here only to be dismissed. The presence of embryonic rests, for example, has rarely been suggested as a cause of carcinoma of the gall-bladder, except in connection with the uncommon squamous epithelioma, and even this remarkable tumour may be explained more convincingly on other grounds. Nor is there any evidence to suggest that heredity plays an important part in the causation of the disease.

FIG. 1.—Multiple papillomata of the gall-bladder. The growths are of benign type, but in places show early invasion of the muscle coat. The condition may be regarded as precancerous.

There remain two factors to be considered: (1) Simple papilloma of the gall-bladder; and (2) Cholecystitis and gall-stones.

Relation to Simple Papilloma.—Simple papillomata are of common occurrence in the gall-bladder. They may be single or multiple, and occur as minute, green polypoid excrescences on the mucous surface. Microscopically they have the characters of papillary, columnar-celled adenomata, and they are generally of quite benign appearance.

That these benign lesions bear any important relationship to carcinoma is highly improbable, as may be judged by the fact that Phillips has recently reported a series of 500 cases with no single instance of malignant degeneration. There are, however, rare cases of multiple papillomata, which appear to form an intermediate link between the simple tumour and the papillary type of malignant growth. The specimen shown in *Fig.* 1 is of this type. In it the gall-bladder mucosa is studded with minute papillomata throughout its whole extent. Microscopic examination showed the growths to be of benign type, but with small areas of epithelial proliferation which extended in places through the muscle coat of the gall-bladder wall. There is a close resemblance between this specimen and the papillary carcinoma shown in *Fig.* 2.

2. **Relation to Cholecystitis and Gall-stones.**—Almost all writers have drawn attention to the striking relation of gall-bladder carcinoma to gall-stones, and have differed only in their estimates of the frequency with which the two lesions coexist. Thus Musser found that in a series of 100 cases of carcinoma of

the gall-bladder stones were present in 69 and definitely stated to be absent in only 3. Fütterer found stones to have been present in at least 70 per cent of the 209 cases he reported, whilst Siegert was of the opinion that stones coexist in 95 per cent of cases.

In the present series of 50 cases, stones were found in 31 and were undoubtedly absent in 7, whilst in the remaining 12 cases the presence of stones could not definitely be determined or had not been recorded.

These figures are highly significant, considering that in control cases of similar ages the incidence of gall-stones is less than 10 per cent, and there can be no doubt that there is a definite relationship between gall-stones and carcinoma of the gall-bladder. That the stones have been present before the carcinoma has originated,

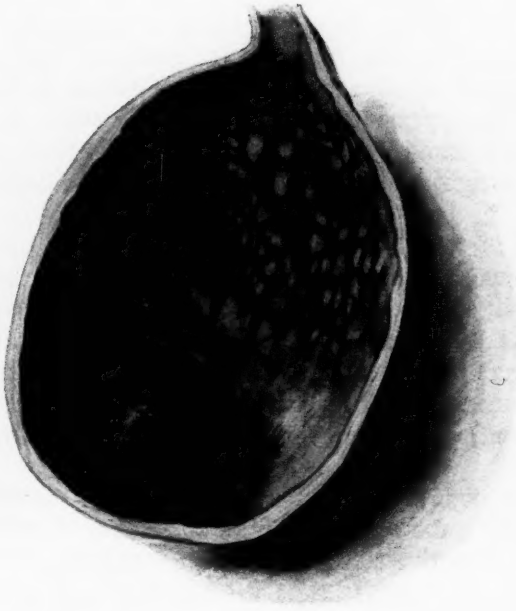


FIG. 2.—An early carcinoma of the gall-bladder of the papillary type. At operation the large gall-stone was found impacted at the neck of the gall-bladder, in contact with the growth.

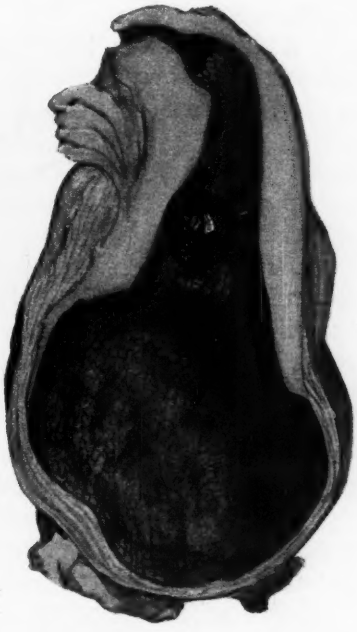


FIG. 3.—Scirrhous carcinoma of the gall-bladder. At operation the solitary stone was found impacted near the neck of the gall-bladder. The viscus was acutely inflamed and contained mucopus.

and are not secondary formations due to the biliary obstruction caused by the growth, is proved by the fact that in most cases the stones are well consolidated, with a structure indicative of long formation. Moreover, in some cases the growth originates at the neck of the gall-bladder where the mucosa is ulcerated by the pressure of an impacted stone (*Figs.* 2, 3).

Several writers have suggested that stones predispose to carcinoma of the gall-bladder in virtue of some special constituent, for it is known that gall-stones contain traces of many minerals, such as copper, iron, and manganese, in addition to cholesterol, calcium, and bile pigments. Lazarus-Barlow has shown that a small proportion of gall-stones contain radio-active salts, and has suggested that the origin of the carcinoma is due to their long-continued irradiation. At present,

however, this view lacks confirmation. Perhaps future researches will demonstrate the presence of a specific agent similar to dibenzanthracene, or the active hydrocarbons occurring in carcinogenic tars.

It is interesting to note that there are a number of cases on record in which a carcinoma has originated several months or even years after the stones have been removed by cholecystotomy. Many years ago Knaggs, Mayo Robson, and Lett recorded single instances of this sequence of events, and several other cases have been reported recently. In 84 gall-bladder carcinomata reported by Magoun and Renshaw there were 5 in which previous cholecystostomy had been performed. In its tendency to occur after the predisposing agent has been removed carcinoma of the gall-bladder is comparable to tar cancer, to the skin epithelioma of mule-spinners and shale-workers, and to other forms of carcinoma arising as the result of chronic irritation.

Whilst attention has been directed mainly to the relation of carcinoma to gall-stones, an even more important predisposing factor is the presence of cholecystitis. There are undoubted cases of carcinoma of the gall-bladder without stones, but a pre-existing cholecystitis appears to be the invariable rule. It is doubtful if carcinoma ever starts in a healthy gall-bladder, and it is thus one of the most perfect examples of a malignant growth arising as a result of chronic irritation.

The risk of carcinoma developing in patients with calculous cholecystitis is by no means inconsiderable, as has been shown by numerous statistics based on experience both in the autopsy department and in surgical clinics. Thus Riedel, in his paper on gall-stones published in 1901, stated that in the course of five or six hundred gall-stone cases seen by him there were no fewer than 43 cases of carcinoma (7 to 8 per cent), whilst Fawcett and Rippmann found that malignant change had supervened in no fewer than 48 (8·1 per cent) of 592 gall-stone cases seen in the autopsy department of Guy's Hospital.

Whilst it is probable that these figures, derived as they are from selected groups of cases—namely, those in which the symptoms were sufficiently severe to necessitate admission to hospital—tend to give a somewhat exaggerated idea of the frequency of malignant degeneration, they nevertheless indicate that the risk is by no means inconsiderable.

From the clinical standpoint it is important that this risk should be fully appreciated. When a carcinoma of the gall-bladder is fully established, there is little prospect of being able to extirpate it completely. Our aim must therefore be to prevent its occurrence, and this can only be achieved by early operation. And since a carcinoma may arise even after removal of the stones, the only certain method of prevention is by the performance of cholecystectomy.

EXPERIMENTAL PRODUCTION OF CARCINOMA OF THE GALL-BLADDER

A number of attempts have been made to produce carcinoma of the gall-bladder in animals, but with little success. This is not surprising, considering that it is notoriously difficult to initiate a carcinoma in any columnar-celled membrane, and especially in view of the fact that spontaneous gall-bladder carcinoma in animals in unknown.

Kazama in 1912 claimed to have produced carcinoma in guinea-pigs by inserting such foreign bodies as pebbles, suture material, and lanoline into the gall-bladder. In a series of 98 guinea-pigs he claimed that cancer was produced in 26.

Leitch repeated these and similar experiments, inserting gall-stones, pebbles, and pilules of pitch into the gall-bladder. When the animals were killed from five to twelve months later, the gall-bladder wall was found to be thickened and indurated, and microscopic examination showed areas that appeared to be carcinomatous. Subsequent work, however, appears to indicate that these lesions were not malignant, and that the epithelial proliferation was simple in type, a response to the chronic irritation of the foreign bodies.

Since then, Clemente, Delbet and Godard, and others have performed similar experiments, using tar, gall-stones from cancerous patients, and other foreign bodies.

Burrows has recently summarized all the literature on this subject and has repeated the experimental work, inserting gall-stones derived from non-cancerous patients into the gall-bladders of guinea-pigs. He points out that there are certain fallacies attending the microscopic diagnosis of carcinoma after such experiments, for the remarkably active proliferation of glandular structures and young bile-ducts as a result of the irritation may easily be mistaken for malignant growth. Burrows' work indicates the need for caution in assessing the previous experimental findings, and the claims of certain workers to have produced carcinoma of the gall-bladder experimentally cannot be regarded as substantiated.

FIG. 4.—Scirrhous carcinoma of the gall-bladder, giving rise to an hour-glass deformity. The greater omentum is adherent to the distal sac, which is obstructed and inflamed.

THE PATHOLOGY OF CARCINOMA OF THE GALL-BLADDER

We may recognize four principal types of carcinoma of the gall-bladder, which may be distinguished from each other fairly readily by either naked-eye or microscopic examination: (1) Scirrhous carcinoma; (2) Papillary carcinoma; (3) Mucoid or colloid carcinoma; (4) Squamous-cell carcinoma or epithelioma.

1. **Scirrhous Carcinoma.**—This is quite the commonest type of growth seen in the gall-bladder. It is a hard infiltrative tumour, which starts as a localized thickening or induration of the gall-bladder wall, and gradually spreads to encircle or ultimately to envelop that viscus. At an early stage it may be mistaken for

an area of chronic cholecystitis, and if, as often happens, it arises in a gall-bladder already thickened and indurated as a result of chronic cholecystitis, it may easily be overlooked unless routine microscopic examinations are carried out. Later, the presence of the growth will be recognized by the degree of induration, for it may be as hard as cartilage.

The growth may originate at the neck of the gall-bladder, at its mid-point, or at the fundus. In the series reported here the growth had started at or close to the neck of the gall-bladder in 6 cases, near the mid-point in 2 cases, and at

FIG. 5.—Scirrhous carcinoma, completely enveloping the gall-bladder and invading the liver. The adherent omentum is infiltrated by the growth, and a secondary nodule is seen in the cystic lymph gland.

the fundus in 3 cases. In the remainder the growth was so extensive that its site of origin could not be demonstrated.

If the tumour arises at the neck of the gall-bladder, it may constrict the cystic duct and lead to a mucocele or an empyema of the gall-bladder, as happened in one of the cases recorded here (*see Fig.* 3). A tumour arising in the body of the gall-bladder may give rise to an hour-glass deformity, as in the case illustrated in *Fig.* 4.

Eventually, a scirrhous growth may infiltrate the whole gall-bladder, enveloping

it completely in a dense mass of malignant tissue (*Fig.* 5). Indeed, the gall-bladder may be so buried in the growth as to be difficult to find, even at autopsy, and the only clue to its situation may be a collection of gall-stones, packed tightly in the centre of the tumour. Sometimes, as the tumour contracts upon the lumen of the gall-bladder, the stones are extruded into the common bile-duct.

FIG. 6.—Scirrhous carcinoma of the gall-bladder. The tumour is an adenocarcinoma, and contains irregular acini lined by columnar and cubical cells.

The microscopic structure of a scirrhous tumour of the gall-bladder is that of an adenocarcinoma (*Fig.* 6). There are acini or tubules, lined by columnar or cubical cells, set in a stroma of dense fibrous tissue. The epithelial cells are often of low columnar type, and evidence of their secretory activity may be furnished by the presence of mucin within the acini.

In most cases the cells are obviously malignant, but in others the appearance is not greatly different from that of the normal cells of the mucosa, and indeed it may occasionally be difficult to distinguish the acini of a carcinoma from the glandular proliferations sometimes seen in chronic cholecystitis—the so-called cholecystitis glandularis proliferans.

FIG. 7.—Papillary carcinoma of the gall-bladder. The tumour was cut across when the gall-bladder was opened, and its two halves are displayed. The tumour is pedunculated and nodular, and to the naked eye appears benign, but its malignant character is evident on microscopic examination.

When it is remembered that acini of a somewhat atypical appearance may penetrate the muscle coat in chronic cholecystitis (the Rokitansky-Aschoff sinuses) and that similar deeply placed tubules are sometimes found in the healthy gall-bladder (Luschka crypts), the difficulty in diagnosing an early carcinoma will be apparent.

2. **Papillary Carcinoma.**—This is less common than the scirrhous growth. It is a softer and often a more bulky tumour, and it

does not infiltrate so extensively, but rather tends to grow into the cavity of the gall-bladder.

At an early stage it may consist of multiple small villous outgrowths of the mucous membrane, rather resembling a malignant papilloma of the urinary bladder. The specimen shown in *Fig.* 2 is of this type. Rarely there is a solitary, pedunculated tumour, which may appear to be benign until examined microscopically (*Fig.* 7). Later the tumour may attain quite considerable size, partly filling the gall-bladder. It is prone to hæmorrhage and necrosis, and may be so soft as to be mistaken for inspissated pus.

The microscopic appearance is that of a columnar-cell adenocarcinoma with a scanty connective-tissue stroma. Often a definite papillary arrangement is recognizable.

3. **Mucoid or Colloid Carcinoma.**—This type of growth is not uncommon in the gall-bladder. The tumour is generally somewhat bulky and soft, and its character may be recognized by the jelly-like appearance of the growth. Sometimes the whole tumour is of mucoid type, more often only a part is affected, and in some cases the condition may only be discovered on microscopic examination. In the present series some degree of mucoid change was observed microscopically in several cases. In only one, however, was it so extensive as to be recognizable on naked-eye examination.

FIG. 8.—Mucoid carcinoma of the gall-bladder. There are a few ill-formed acini lined by columnar cells, scattered like small islands in a sea of mucin.

Microscopically there is a stroma consisting of trabeculæ of fibrous tissue, interspersed with large spaces containing a structureless, blue-staining material—pseudomucin. The tumour cells are few in number and lie singly or in small groups or ill-formed acini, often scattered like small islands in a sea of mucin (*Fig.* 8). The cells contain small droplets of mucin in their cytoplasm, and some of them are swollen to 'signet-ring' shape by a large globule of this substance, which distends the cell membrane and forces the nucleus to one edge. A cell thus distended may burst, discharging its mucinous content into the connective-tissue spaces.

4. **Squamous-cell Carcinoma or Epithelioma.**—This remarkable tumour is the least common form of gall-bladder carcinoma. In the present series of 30 cases there was only one complete example—that is, one in which all parts of the tumour were of squamous character. In two other cases a partial squamous-cell change had supervened, giving rise to the extraordinary appearance of areas of squamous epithelioma adjoining and merging into areas of columnar-cell adenocarcinoma.

To the naked eye, tumours of this class generally appear of scirrhous infiltrating character, and the peculiar nature of the growth is only recognizable on histological examination.

Microscopically, parts of the tumour, or in some cases the entire growth, present the characters of an epithelioma, such as are seen in tumours of the skin, the tongue, or the œsophagus. The cells are of squamous type, and it is some-

FIG. 9.—Squamous-cell carcinoma of the gall-bladder showing typical cell-nest formations. (× 120.)

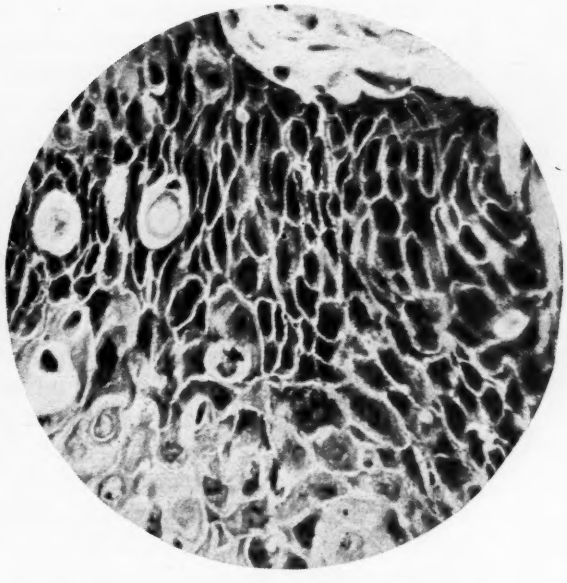


FIG. 10.—Squamous-cell carcinoma of the gall-bladder showing the presence of prickle cells with intercellular bridges. (× 400.)

times possible to identify typical prickle cells with intercellular bridges. Cell nests or epithelial pearls occur, though rarely, for keratinization is not a marked feature of these tumours (*Figs.* 9, 10).

The special interest of squamous epithelioma of the gall-bladder lies in the fact that it occurs in a columnar-cell epithelium derived from entoderm. The gall-bladder is derived by a process of budding from the biliary diverticulum, which arises from the intestine at the junction of foregut and midgut, and at no period of embryonic life is it related to a squamous-cell membrane.

There is therefore no reason to attribute an epithelioma of the gall-bladder to the persistence of epithelial rests of squamous type, nor is there, at first thought, any explanation based on embryological grounds.

It seems probable that epithelioma in the gall-bladder should be regarded as

the result of a process of metaplasia, whereby the cells of the mucous membrane, originally cylindrical, have reverted to their primitive form and subsequently assumed squamous characters.

Nicholson has pointed out that such a change has its analogy in the normal development of the œsophagus. The œsophagus is derived from the primitive foregut, and, as Schaffer and Keibel have shown, its lining membrane, like that of the remainder of the foregut, originally consists of a layer of ciliated cylindrical cells. Whereas in the remainder of the foregut the cells retain their cylindrical form, in the œsophagus at an early stage in embryonic life they are entirely converted to squamous type. This potentiality for squamous metaplasia, normally seen only in the œsophagus, is found occasionally in the cells of the cardiac end of the stomach, and it is quite conceivable that it may be retained in exceptional cases by the cells of the lower part of the foregut close to the point from which the gall-bladder is derived.

The customary explanation of epithelioma of the gall-bladder is that it arises in a part of the gall-bladder wall affected by leukoplakia. As a result of chronic irritation by gall-stones or cholecystitis, the epithelial cells of the mucous membrane assume squamous form, whilst further irritation leads to their developing malignant characters.

THE SPREAD OF CARCINOMA OF THE GALL-BLADDER

In the great majority of cases carcinoma of the gall-bladder spreads by direct invasion of neighbouring viscera and regional lymph-vessels. The growth disseminates to distant organs rarely, even in its terminal phase; quite early in its course, however, it invades locally and oversteps the limits of successful removal.

The *liver* is generally the first organ to be invaded. It was involved in all the 14 cases of the present series examined post-mortem and in 12 of the 16 cases seen at operation. In the remaining four cases there were no evident metastases, and in each the gall-bladder was removed.

Generally the tumour spreads by direct continuity from the gall-bladder to the adjoining part of the right lobe of the liver and forms there a solitary, hard, and often bulky mass. The remainder of the liver is usually unaffected, but in a small proportion of cases there are multiple secondary nodules scattered through both lobes. Less often the liver is invaded by a branching growth spreading along the periportal lymph-vessels from the lymph nodes in the porta hepatis.

The *regional lymph nodes* are involved almost as often as the liver, and their involvement may preclude successful operation in cases where the extirpation of a localized mass invading the liver might otherwise be attempted.

The cystic lymph node, which lies on the under aspect of the cystic duct, is involved first, and from there the disease spreads to the nodes in the right free border of the lesser omentum, in the porta hepatis, and in the retroperitoneal tissues. In many cases the jaundice observed in carcinoma of the gall-bladder is due to the pressure of secondary nodes upon the common bile-duct. In autopsy cases lymph-borne metastases are occasionally found in the mediastinal, tracheobronchial, and even the cervical lymph nodes.

The *peritoneum* is involved quite often in the later stages of the disease. It is said that this is most likely to occur when the tumour is of mucoid type. Multiple

secondary nodules then develop on the peritoneal surfaces and malignant ascites rapidly supervenes. There is one case on record (Wakasugi) in which a large metastasis on the pelvic floor simulated a carcinoma of the rectum.

The *omentum* is involved in a number of cases, especially if it be adherent to the gall-bladder as a result of cholecystitis.

The *duodenum*, the *colon*, and even the *jejunum* may be involved by direct invasion, and fistulæ between the gall-bladder and these viscera are not uncommon. In some cases when invasion of this type occurs early the clinical features may suggest the presence of a primary tumour at the pylorus or in the right colic flexure.

Distant metastases are uncommon, even in autopsy cases. There are a few instances on record, however, in which distant metastases have occurred so early in the course of the disease as to provide the first clinical evidence of it.

The *lungs* are involved in about 10 per cent of cases. The pulmonary metastases are generally multiple, of small size, and mainly situated close under the pleura. The growths are most numerous in the lower lobe of the right lung, and it seems probable that they reach that situation by spreading along the retro-diaphragmatic lymphatics.

In one case, reported recently by Foggie and Tudhope, there was a solitary metastasis in the upper lobe of the left lung. In this case the primary tumour was inconspicuous, and was discovered only at autopsy. In a case reported by Osler in 1906 a nodule in the right breast, which simulated a primary mammary carcinoma, was the first demonstrable evidence of the disease.

The *bones* have been the site of metastatic growth in a few reported instances. Beadles in 1897 reported a case in which the first evidence of disease was provided by a tumour arising in the second rib. The tumour increased in size during four months, infiltrating the pectoral muscles but not invading the pleura, and eventually it attained the size of a coco-nut. Only at post-mortem examination was the primary growth found.

CLINICAL FEATURES

Since carcinoma of the gall-bladder is almost invariably imposed upon a former cholecystitis, generally with gall-stones, we should expect that in the majority of cases an old history of biliary disease would be forthcoming. Such a history was obtained in 16 of the 30 fully recorded cases in the present series, dating back five, ten, or even thirty years. In the majority the symptoms were of the type generally associated with chronic cholecystitis—flatulent indigestion, pain below the right costal margin, and occasional attacks of biliary colic. In several cases there had been one or more attacks of jaundice. In one case cholecystostomy had been performed seven years before.

It is surprising that in as many as 14 cases no history of previous disease was obtainable, and this is in accord with the observations of other writers. To some extent, doubtless, this is due to faulty anamnesis. Leading questions are required to elicit a history of relatively mild digestive upset, in a patient in the late stages of malignant disease. In this connection it is noteworthy that, in the present series, a former history of biliary disease was obtainable much more frequently in the surgical cases than in those seen at autopsy. Even allowing for this, however,

there remains a certain proportion of cases in which a previous history is entirely lacking.

Typical Cases.—In typical cases a carcinoma of the gall-bladder gives rise to pain, associated with anorexia, nausea, and vomiting, and followed by jaundice, whilst examination may reveal a palpable swelling under the right costal margin.

The pain is at first not severe, and may be regarded merely as indigestion. It is generally of dull, aching, or gnawing nature, continuous, and unrelated to food. It is situated over the gall-bladder region, and in most cases radiates to the right scapula or the loin. Occasionally, referred pain is felt in the left hypochondrium or in the lower part of the abdomen, whilst in rare cases there is a definite history of pain at the tip of the right shoulder. The pain is rarely colicky, but in the late stages is often severe. In a few cases, however, pain is not a prominent feature. In two cases in the present series the disease was painless throughout.

Nausea was a recorded symptom in every case. Vomiting occurred in most cases, but was rarely severe or persistent. Anorexia, flatulent distension, and occasionally diarrhœa were other features.

Jaundice was noted at some stage of the disease in 16 of the 30 cases. Typically, it is of late occurrence, due to pressure by secondary growths upon the common duct. It is important to observe that jaundice is not necessarily a bar to successful operation. In two cases in the present series the jaundice was due to the presence of stones in the duct—in one of these the growth was limited to the gall-bladder and was removed—whilst in a third the jaundice was due to cholangitis, with multiple liver abscesses.

A palpable swelling in the subcostal region is a frequent finding in the late stages of the disease. It was noted in 18 of the 30 cases in the present series. Generally the swelling is of stony hardness and is due to the growth itself, enveloping the gall-bladder and infiltrating the liver. Less often the swelling is due to mucocele or empyema of the gall-bladder behind a tumour located near the cystic duct.

It is important to recognize that loss of weight is not a common finding in carcinoma of the gall-bladder. The tumour may attain large size and spread extensively with little or no disturbance of the general nutrition. Pronounced loss of weight was noted in only 8 of the 30 cases, whilst in 11 cases it was definitely stated that no loss of weight had occurred, and in many of the remainder the patient was noted as well-nourished, stout, or even obese.

Atypical Cases.—The present series includes a number of cases in which the symptoms differ from those described above, and many others are recorded in the literature. For convenience, they may be divided into three groups.

1. *Symptoms Mainly Due to Obstruction of the Common Duct.*—Five of the present series fall into this group. The primary growth is symptomless or almost so, and the clinical features are mainly due to pressure by the growth or by metastatic nodules upon the common duct. In these cases jaundice is an early feature. It is painless in onset, progressive in course, and ultimately intense. Since the gall-bladder may be palpably enlarged, the condition is apt to be mistaken for carcinoma of the pancreas or of the common duct. The progress in these cases is rapid, and death may occur within a few weeks of the onset of the jaundice.

2. *Symptoms Mainly Due to Obstruction of the Cystic Duct.*—Three of the thirty

cases fall into this group. They are exemplified by the following case, in which the clinical features were those of empyema of the gall-bladder. A woman aged 62 years, who gave an old history of biliary trouble, was admitted to hospital with acute pain in the right subcostal region, radiating to the back. There was slight pyrexia, no jaundice. Abdominal examination revealed an enlarged, very tender gall-bladder, protected by muscular boarding. At operation the gall-bladder was distended, inflamed, and surrounded by soft omental adhesions. It was opened and found to contain mucopus and a single stone, impacted at the neck. Further examination revealed the presence of the growth, and accordingly the gall-bladder was removed. (*See Fig.* 3.)

3. *Symptoms Mainly Due to Secondary Growths.*—In five cases in the present series the first symptoms were due to secondary growths. In two of these widespread peritoneal metastases gave rise to abdominal pain mainly located in the umbilical region and the lower part of the abdomen, with vomiting, diarrhœa, ascites, and rapid progress to a fatal issue. In one case a secondary growth invading the duodenum gave rise to pyloric obstruction with hæmatemesis and melæna. In two cases the symptoms appeared to be due to widespread involvement of the liver, and were characterized by repeated retching and vomiting, with pain over the enlarged liver, slight jaundice, and marked toxæmia.

TREATMENT AND PROGNOSIS

At the present time the majority of cases are seen too late for radical removal of the tumour, and although it is sometimes possible to relieve the symptoms to some extent either by draining the gall-bladder if distended, or by establishing biliary drainage if the common duct is compressed, such procedures can clearly be of limited value.

The probable duration of life in such cases is generally short. The immediate mortality alone is high, for in many cases jaundice is present at the time of operation and cannot be relieved. Those who survive the immediate post-operative period generally succumb within a few months.

In a small proportion of cases, however, where the growth is found at an early stage, the results of surgical treatment are more satisfactory. If the growth is limited to the gall-bladder wall, complete extirpation may be achieved, whilst even when there is local invasion of the liver, excision of the affected portion of that viscus may be carried out. It must be admitted, however, that this is only rarely possible.

The difficulty of treating an established carcinoma of the gall-bladder emphasizes the importance of preventing its occurrence by radical treatment of its main etiological factor, calculous cholecystitis. When it is borne in mind that malignant disease is the eventual outcome in a by no means inconsiderable proportion of all gall-stone cases, it will be seen that the benefits of timely operation far outweigh the risks. The observation that carcinoma may develop years after the stones have been removed by cholecystostomy indicates that removal of the gall-bladder is the operation of choice.

This paper is the outcome of work carried out in the Department of Surgery of the University of Edinburgh, and is based upon cases seen in the Edinburgh

Royal Infirmary and Western Hospital. The writer wishes to acknowledge his debt of gratitude to Professor D. P. D. Wilkie for permission to make use of his cases, and for his constant encouragement in the production of the paper; to the staff of the Department of Surgery for their technical co-operation; and, lastly, to Colonel W. F. Harvey, of the Laboratory of the Royal College of Physicians of Edinburgh, for the use of the excellent photomicrographs illustrated in *Figs.* 9 and 10.

BIBLIOGRAPHY

AMES, D., *Bull. Johns Hopkins Hosp.*, 1894, v, 74.
BAILLIE, MATTHEW, *The Morbid Anatomy of Some of the Most Important Parts of the Human Body*, 1833, 203.
BEADLES, C. F., *Trans. Pathol. Soc., Lond.*, 1897, xlviii, 119.
BURROWS, H., *Brit. Jour. Surg.*, 1933, xx, 607.
CLEMENTE, G., *Arch. ital. di Chir.*, 1927, xvii, 613.
COURVOISIER, L. G., *Beiträge zur Pathol. u. Chir. der Gallenwege*, 1890. Leipzig.
DEAVER, J. B., *Med. Record*, 1919, xcvi, 47.
DELBET, P., and GODARD, H., *Bull. pour l'Etude du Cancer*, 1928, xvii, 347.
FAWCETT, J., and RIPPMANN, C. H., *Guy's Hosp. Rep.*, 1913, lxvii, 41.
FOGGIE, W. E., and TUDHOPE, G. R., *Edin. Med. Jour.*, 1930, xxxvii, 632.
FRERICHS, F. T., *Clinical Treatise on Diseases of the Liver*, 1861, ii, 479.
FÜTTERER, G., *Ueber die Aetiologie des Carcinoms*, 1901. Wiesbaden.
HALLE, *Hist. de la Soc. de Méd., Paris*, 1786–90, 125.
JUDD, E. S., and GRAY, H. K., *Surg. Gynecol. and Obst.*, 1932, lv, 308.
KAZAMA, Y., *Japan Med. World*, 1922, ii, 309.
KEIBEL, F., *Arch. f. pathol. Anat.*, 1904, clxxvii, 368.
KNAGGS, R. LAWFORD, *Lancet*, 1904, i, 1054.
LAZARUS-BARLOW, W. S., *Proc. Roy. Soc. Med.* (Sect. Pathol.), 1917, xi, 1.
LEITCH, A., *Brit. Med. Jour.*, 1924, ii, 451.
LENTZE, F. A., *Beitr. z. klin. Chir.*, 1926, cxxxvii, 38.
LETT, H., *Lancet*, 1909, i, 1099.
MAGOUN, J. A. H., and RENSHAW, K., *Ann. of Surg.*, 1921, lxxiv, 700.
MAYO ROBSON, A. W., *Diseases of the Gall-bladder and Bile-ducts*, 1897, 42. London.
MOXON, W., *Trans. Pathol. Soc. Lond.*, 1867, xviii, 140.
MUSSER, J. H., *Boston Med. and Surg. Jour.*, 1889, cxxi, 525, 553, 581.
NICHOLSON, G. W., *Jour. Pathol. and Bacteriol.*, 1909, xiii, 41.
OSLER, W., *Brit. Med. Jour.*, 1906, i, 2.
PHILLIPS, J. R., *Amer. Jour. Surg.*, 1933, xxi, 38.
PROESCHER, F., *Jour. Amer. Med. Assoc.*, 1907, xlviii, 481.
RIEDEL, B., *Berl. klin. Woch.*, 1901, xxxviii, 1, 40, 78.
SCHAFFER, J., *Arch. f. pathol. Anat.*, 1904, clxxvii, 181.
SHELLEY, H. J., and ROSS, L. I., *Arch. of Surg.*, 1932, xxv, 65.
SIEGERT, F., *Arch. f. pathol. Anat.*, 1893, cxxxii, 353.
SMITHIES, F., *Amer. Jour. Med. Sci.*, 1919, clvii, 67.
STOLL, MAXIMILIAN, *Pars Prima Rationis Medendi*, 1777, i, 290. Vienna.
WAKASUGI, K., *Beitr. z. pathol. Anat.*, 1910, xlvii, 483.

THE OPERATIVE TREATMENT OF FIBROUS STRICTURE OF THE RECTUM:

WITH THE DESCRIPTION OF A NEW TECHNIQUE

By J. P. LOCKHART-MUMMERY
EMERITUS SURGEON, ST. MARK'S HOSPITAL, LONDON

AND O. V. LLOYD-DAVIES
ASSISTANT SURGEON, ST. MARK'S HOSPITAL

SIMPLE, or fibrous, strictures of the rectum are met with in very many different forms, but all the cases can be roughly divided into two main types, tunnel strictures and ring strictures.

Fibrous strictures of the rectum result from the contraction of scar tissue caused by injury or severe inflammation in the rectal wall or the tissues immediately around it. The contracting scar tissue may be localized to one particular part of the rectum, and result from accidental or operative trauma, or from a localized ulcer or abscess, or it may be due to a general inflammation of the rectum and surrounding tissues. Any of the ordinary forms of septic infection may be responsible for the condition, and there are also certain more or less specific forms of infection such as gonorrhœal infection of the rectum, tertiary syphilis, and fourth disease or lymphangitis inguinale.

We do not propose to discuss here the etiology of rectal stricture, or the difficult question of the relation of syphilis to the condition, beyond saying that it is now generally agreed that syphilis is a very rare cause and that antisyphilitic treatment seldom results in any improvement, though in doubtful cases it should be given a trial before proceeding to operative interference. Whatever the original cause may have been, the condition which the surgeon is called upon to treat is a late result of old-standing inflammation. As a rule it is only after a long period of chronic inflammation, often lasting several years, that the stricture becomes sufficiently severe to call for operative interference.

The diagnosis is not always easy, and it is important to ascertain the type of stricture and its extent. It is generally advisable to administer an anæsthetic, preferably a low spinal injection, and then partly to dilate the stricture so that its upper limits can be explored and the condition of the bowel immediately above ascertained. A very fine bore sigmoidoscope can usually be passed through the stricture and the condition of the bowel above investigated. Needless to say, great care must be exercised not to split the rectal wall and set up a perirectal inflammation. There is almost always in cases of old stricture a severe degree of local sepsis present, and before proceeding to any operative attack upon the stricture this must be cleared up as far as possible. The stricture should be dilated as much as is safe and treated by frequent douching with mild antiseptics. In very severe cases a preliminary temporary colostomy will be necessary.

ANNULAR DIAPHRAGMATIC STRICTURE

The choice of treatment will depend very largely upon the situation of the stricture. If it is situated at the anus or in the lower part of the rectum, below the peritoneal reflection, it can be dealt with comparatively easily. The best method is by internal proctotomy and dilatation. The stricture is nicked with a blunt-pointed bistoury in several places posteriorly and laterally, but not anteriorly, and then rapidly dilated up to an inch in diameter with metal dilators. The rectum is then thoroughly washed out with antiseptic, and partly filled with sterilized vaseline. A large rectal tube, preferably of vulcanite, of the same size as the largest rectal dilator is inserted into the rectum and retained for two days. After this the stricture is kept dilated by passing a full-sized dilator, at first daily and then at longer and longer intervals. This should continue for about three months until all sign of stricture has disappeared.

The results of internal proctotomy are excellent and permanent, if the patient is willing to put up with the inconvenience of dilating the site of the stricture for long enough to counteract the tendency to recurrent contraction in the scar tissue. This is the method that has been used for years at St. Mark's Hospital for this type of stricture, and the results have been uniformly satisfactory.

This method is not applicable where the stricture is very high up and near, or above, the peritoneal reflection, as there would be serious risk of tearing the bowel into the peritoneal cavity. In the case of a thin diaphragm stricture situated high up, internal proctotomy can sometimes be performed successfully if great care is taken and the cutting of the diaphragm is done visually through an operating sigmoidoscope. The dangers of dilating high-lying strictures of the rectum are so serious that such treatment is best not attempted. High strictures are best treated by resection or colostomy, or by the plastic method described here.

TUNNEL STRICTURES

This type of stricture (*Fig.* 11) cannot be dealt with by internal proctotomy, and dilatation is very unsatisfactory, as it involves the constant use of dilators, usually with little benefit and much pain. The alternatives are permanent colostomy, resection of the strictured portion of the rectum, and, in suitable cases, the method described here. Colostomy is sometimes the only possibility, and, where a serious degree of stricture with bad local sepsis exists, may have to be permanent. In most cases a temporary colostomy is the first step in the procedure, and if there is a possibility of restoring the rectum a transverse colostomy should be performed, both because it is more easily and safely closed again, and because it leaves the pelvic colon free to be brought down if a resection of the stricture is to be performed later.

The best known method of resecting a rectal stricture is that of Hartmann. The rectum is exposed through a posterior incision after removing the coccyx. The bowel is then divided above the stricture and dissected out to the skin margin at the anus without damaging the sphincter, and the proximal end of the colon is brought down and fixed to the skin at the anal margin. Hartmann records 34 cases treated by resection, with 2 deaths.

The chief difficulty of the resection operation is to get the parts sufficiently

free from gross sepsis to render any operation reasonably safe. There is often a free discharge of pus from the rectum, and numerous fistulæ discharging on the skin surface. A preliminary colostomy, followed for some weeks or months by frequent irrigation of the strictured bowel from the lower colostomy opening, will often clear up the septic condition sufficiently to make operation on the stricture

FIG. 11.—Drawing of a specimen of fibrous stricture of the rectum in the Royal College of Surgeons Museum, showing dense fibrosis of the perirectal tissues.

possible (*Fig.* 12). Even then the operation is by no means easy owing to the dense fibrous tissue present in the cellular tissues around the bowel that has to be removed. The combination of sepsis and fibrous adhesions round the bowel render the operation of resection more difficult in cases of fibrous strictures than in malignant disease.

NEW TECHNIQUE

In the following case a procedure was adopted which we believe to be original and seems to offer an alternative to Hartmann's method of resecting the stricture. It has the merit of being both simpler and safer, and, at any rate in this case, gave a better result than could have been obtained by resection. It is obvious that it is not applicable in all cases of fibrous stricture of the rectum, as it is essential that free access should be obtainable to the whole of the strictured area. On the other

hand, since the operation does not involve opening the peritoneum, it is very much safer than a resection operation.

HISTORY.—The patient was a married woman, aged 32. Thirteen years ago, after a bad confinement, she had a profuse discharge of blood and pus from the rectum, associated with abdominal pain and fever. The discharge failed to respond to any treatment, and some years later she was found to be suffering from a severe rectal stricture. Various attempts were made to dilate the stricture without success, and six years ago a colostomy was performed in the pelvic colon. After this the discharge from the rectum gradually ceased, and her general health much improved, but she became very desirous of getting rid of the colostomy opening. She was admitted to St. Mark's Hospital in the hope that something could be done to the stricture to enable the colostomy to be closed.

FIG. 12.—Photograph of a specimen of fibrous stricture of the rectum. The patient was a woman aged 40. The strictured portion of the rectum was resected and the rectum restored after a temporary colostomy. She has remained well since.

ON EXAMINATION.—A well-marked tubular stricture was found about 3 in. in length and situated in the middle and upper part of the rectum. The mucous membrane lining the stricture was ulcerated, but the mucous membrane above, as seen by passing a small sigmoidoscope through the lower colostomy opening, was normal in appearance, as was that of the lower rectum.

An attempt was then made to heal the ulceration by introducing 4 oz. of a suspension of bismuth subgallate (5 per cent) in cotton-seed oil into the lower colostomy opening each night, and washing through every day with a solution made by adding 1 drachm containing equal parts of sodium chloridi, sodium bicarbonatis, and pulv. ac. borici, to one pint of water. At the end of three weeks examination showed that the ulceration had healed, and it was decided to operate on the stricture

by dividing it longitudinally from behind and suturing it in a transverse manner similar to the method used in performing a pyloroplasty for stricture of the pylorus.

OPERATION (*Fig.* 13).—The patient was given a low spinal anæsthetic and then placed in the Sims position. The rectum was thoroughly washed out with a weak antiseptic solution and an incision was made in the mid-line posteriorly, extending from a point over the lower part of the sacrum to a point just behind the anal orifice. The coccyx was removed and the post-rectal fascia divided. The rectum was then freely mobilized by stripping it from the pelvic wall on each side. In this way it was possible to draw down into the wound that part of the rectum containing the stricture. A considerable amount of dense fibrous tissue had to be divided before the actual rectal wall could be exposed, and the stricture was then divided longitudinally into the rectum, the incision extending into healthy bowel both above and below the narrowed portion. Tissue forceps were then placed on the edge

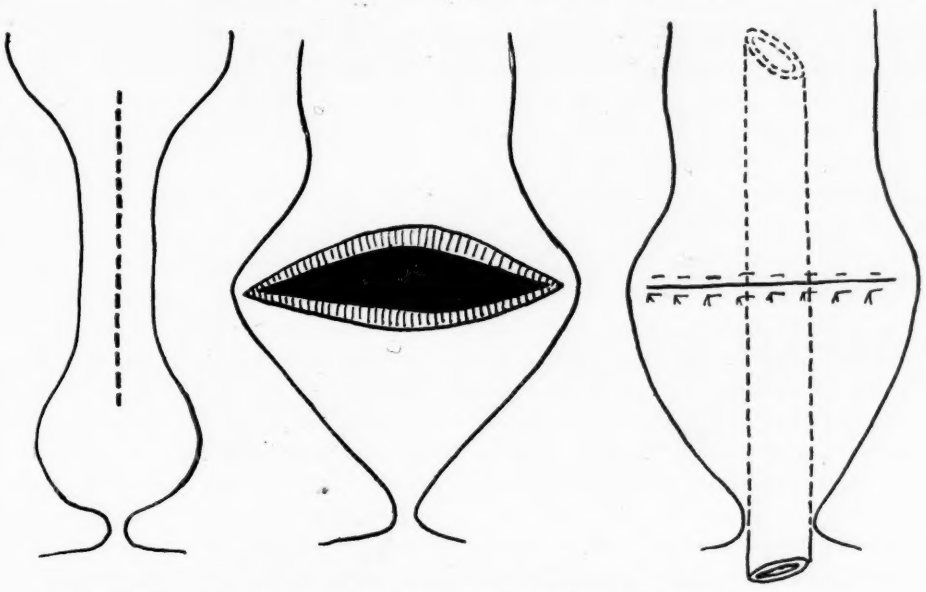


Fig. 13.—Diagram showing steps of the operation for dealing with stricture of the rectum.

of the rectal wound on each side in the middle of the longitudinal incision and the rectum was drawn open. A large rubber tube was next passed into the rectum through the anus, the upper end passing well above the strictured area. The incision in the rectum was then closed transversely by interrupted catgut sutures with the knots on the mucous side, and covered by a second line of Lembert sutures. The fascia was then stitched over the line of suture and the skin closed, a small drain being placed in the upper part of the wound. The drainage tube in the wound was removed in twenty-four hours and the rectal tube in four days. Satisfactory healing took place except for a small sinus, which healed in a few weeks. On examination of the rectum no sign of stricture was present and it was possible to pass a No. 26 Hegar dilator very comfortably and with no pain.

SUBSEQUENT HISTORY.—The patient went home, and returned four months later for closure of the colostomy. The rectum was still well dilated, there was

no sign of stricture, and the colostomy was closed intraperitoneally. The abdominal wound healed very satisfactorily, and the patient returned home three weeks later.

It is now a year since the closure of the colostomy, and the patient's bowels are open normally and regularly every day, and there is no sign of the original stricture.

We have not been able to find any description of a similar operation for fibrous stricture of the rectum, and believe that this is the first time this operation has been performed. The result is so eminently satisfactory that we consider it worth while publishing. It is obviously a much less severe operation than a resection of the rectum, and is not particularly difficult. It has the great merit of leaving the patient with a normally functioning rectum and perfect control, since there is no damage to the muscles of the anal opening.

In order to be successful it would seem essential that all local sepsis should be cleared up before performing the operation, and a temporary colostomy would seem advisable. In performing the operation, the rectum must be thoroughly freed so that no tension will come on the sewn-up wound in the rectal wall.

NOTOCHORDAL TUMOUR OF THE CAUDA EQUINA IN A CHILD OF 8 YEARS

By V. H. ELLIS
ORTHOPÆDIC SURGEON TO ST. MARY'S HOSPITAL, LONDON

Tumours of the notochordal remnant have attracted increasing attention during the last few years, and the diagnosis and treatment of tumours of the spinal cord have also made great advances. The following case, therefore, may have points of interest under both these heads.

The derivation of tumours from the notochord was established by Ribbert[1] in 1894, but the groundwork for his researches was laid by Muller[2] in 1858, and there are records of earlier observations. Since that time many cases have been described and several reviews of the subject published, such as that by Stewart[3] (1926).

The site of the great majority of tumours described has been occipital or sacro-coccygeal, the former arising in connection with the anterior, and the latter with the posterior, extremity of the notochord. Aberrant notochordal vestiges have occasionally been found, and Coenen[4] published a review of such cases in 1925. Unlike chordomata, these tumours are not neoplastic, and have been called 'ecchordoses physaliphoræ'. In the same year Stewart gave this description of ecchordoses: "They are soft, transparent, jelly-like nodules attached by a more or less slender pedicle to the middle of the dorsum sellæ. They project through an aperture in the dura mater and often become loosely attached to the pia arachnoid covering the pons. They are in no sense infiltrative, and cannot be said to show any evidence of active growth."

The tumour to be described, growing from a thin pedicle in the theca, suggests an origin from one of these ecchordoses physaliphoræ. But whereas ecchordoses are very soft, colourless, and transparent, this tumour was firm, purple, and translucent.

CASE REPORT

History.—Elsie C., 8 years of age, was admitted into hospital on Jan. 8, 1934, complaining of pain and stiffness of the back. Four months previously she had had a heavy fall on to her back, but it did not necessitate rest in bed. She had subsequently had pain in the thighs, mostly at night. Shortly before admission she had pneumonia.

On Examination.—The child was seen to be pale and in poor general health, with wasted musculature. The back showed a very marked left-sided scoliosis, with rotation involving the whole of the dorsal and lumbar spine. On standing the scoliosis could be made to disappear, and was apparently due to spasm of the spinal muscles on the right side. Hips and knees were normal, with no individual

muscle weakness and no tenderness or neurological signs. Standing and movements of the spine caused pain in the right thigh.

A provisional diagnosis of tuberculosis of the dorso-lumbar spine was made, but a series of X-rays showed no bony lesion.

Feb. 17.—Mantoux and von Pirquet tests were negative, but the child was kept under observation for another three months, there still being pain and rigidity in the dorso-lumbar region, particularly on the left side. Examination under anæsthesia revealed nothing abnormal in the abdomen, and the blood-count was normal.

FIG. 14.—Shows that the block extends from the top of L 2 to the middle of L 4, where the lipiodol appears to be partially surrounding a nodule. The thecal obstruction is transparent to X rays.

May 25.—The left knee-jerk and ankle-jerk were found to be exaggerated, while the left plantar reflex was extensor. The right side was normal. Sensation in the left lower limb was normal.

May 28.—Lumbar puncture yielded 5 c.c. of straw-coloured fluid, the pressure at first being high, but falling rapidly until no further fluid was obtained. Report on cerebrospinal fluid :—

Proteins	3 grm.
Chlorides	672 mgrm. per 100 c.c.
Sugar	60 mgrm. per 100 c.c.
Lymphocytes	8 per c.c.

June 1.—Lumbar and cistern punctures were performed, with injection of light and heavy lipiodol respectively. X-ray shown in *Fig.* 14.

OPERATION (June 16).—Laminectomy was performed, and the laminæ of L2, 3, and 4 removed. The dura was found to be bulging, and a dark-coloured tumour could be seen through it. The dura itself appeared normal. The appearance on opening the dura is shown in *Fig.* 15.

The tumour was purple and lobulated, and appeared gelatinous. Its only attachment was a slender thread from its caudal part running down towards the sacral theca. This was crushed and divided, and the tumour removed, without injury to the cauda equina.

The child made an uneventful recovery.

SUBSEQUENT HISTORY.—

July 2.—There was no pain or spasm, no symptom. Sensation normal. Reflexes :—

Plantar		R. Extensor	L. Flexor
Knee-jerk	..	nil	++
Ankle-jerk	..	nil	+
Abdominal	..	+	+

Sept. 7.—The child was walking normally with no symptoms. The right plantar reflex was still extensor, and the tendon reflexes were diminished on the right side.

Oct. 12.—As above.

I have been unable to correlate the neurological findings either with the original site of the tumour or of some subsequent recurrence.

PATHOLOGY. — On naked-eye examination the tumour was encapsuled, smooth and lobulated, purple in colour, and translucent (*Fig.* 16). It measured 4 cm. in length, 2·4 cm. in width, and 2 cm. in thickness. No large or well-defined blood-vessels were detected entering the growth. Near its lower pole, which consisted of a rounded lobule, was its pedicle. This was a white thread, about 1 mm. in diameter—that is, about the size of the nerve-roots of the cauda equina. The pedicle ran downwards and forwards towards the sacrum, but its origin was not determined.

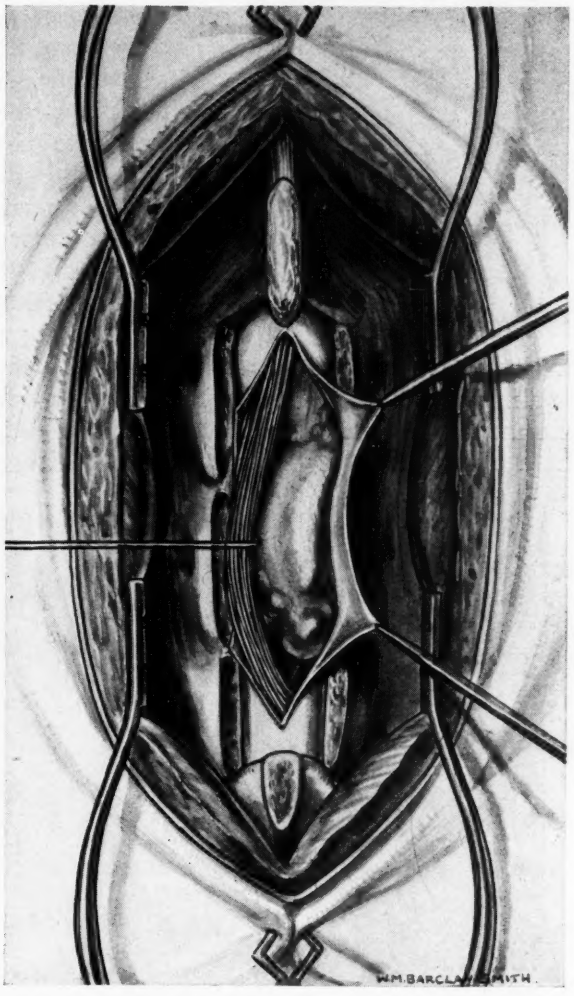


FIG. 15.—Appearance on opening the dura.

MICROSCOPICAL APPEARANCE. — The capsule of the tumour is thin and fibrous. In parts it is œdematous and separated from the tumour by small extravasations of blood. From it narrow fibrous trabeculæ containing numerous blood-vessels divide the tumour into lobules.

The cells forming the growth are epithelial in type and are arranged irregularly. In some parts (*Fig.* 17 *a*, *c*) they are closely packed in sheets with little or no intercellular substance, while in others they are in narrow trabeculæ, tubes, short strands, or even single cells separated by much mucinous material, and there

are all grades of variation between these extremes. In shape they vary from long spindles to polyhedra and spheroids. In the more cellular parts the protoplasm is uniformly stained by acid dyes. Everywhere, however, a certain number of vacuolated cells can be seen, and in the less cellular parts they are very numerous. Some are very large, forming the so-called 'physaliphorous cells' typical of chordomata. Mucin is present only occasionally in these cells. A very small number contain a few globules of fat, but most of the vacuoles are unstainable. As this material was received already fixed in formol saline, any glycogen which may well have been present would have dissolved out in this fixative.

FIG. 16.—Naked-eye appearance of tumour (× 1½.)

The nuclei also vary considerably. In the more cellular parts they are oval and vesicular with well-marked nuclear membranes and poorly-staining chromatin network. Most contain an eosinophil nucleolus, while some have two nucleoli. A few cells have two nuclei and many are hyperchromatic. Only two mitotic figures were seen in a careful search of twelve sections. In the more mucinous parts the nuclei are smaller and stain darker, and in many cells they have disappeared. A few vacuolated nuclei have been seen.

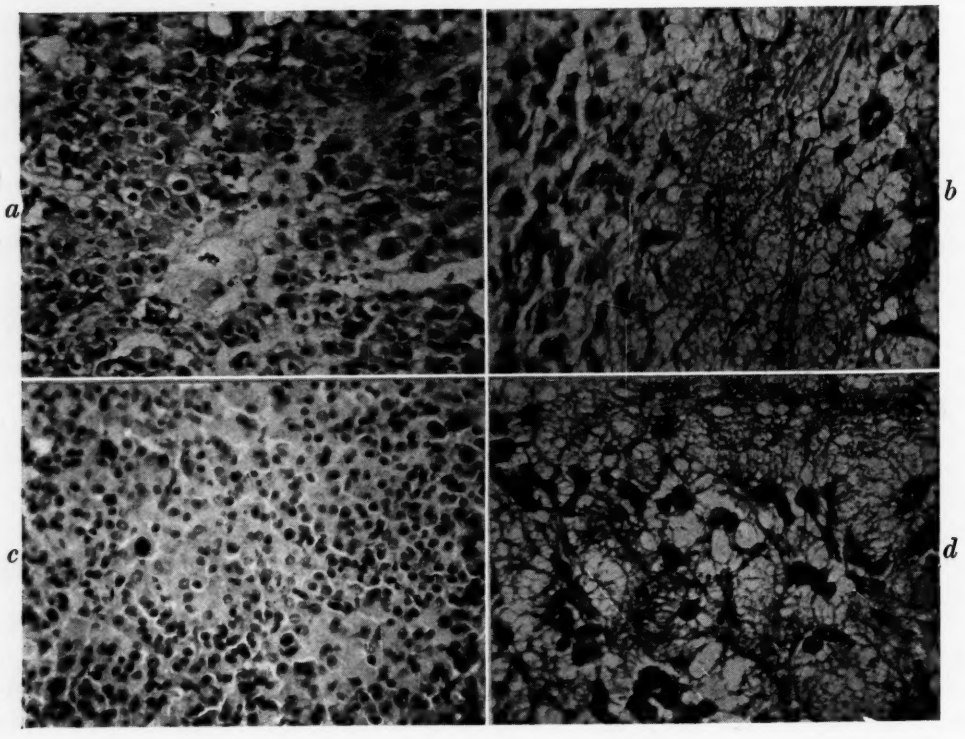


FIG. 17.—Microscopic appearance of tumour.

The mucin in this tumour is nearly all intercellular and is present in large amounts. As in Cappell's[5] *Case* 2 (1928) it is variable in its staining properties. With hæmatoxylin and thionin it is difficult to see, and mucicarmine and polychrome methylene blue will only stain it in parts. Toluidine blue demonstrated it most clearly, and the best metachromatic contrast could only be seen by examining the slide while wet in water. *Fig.* 17 *b* and *d* show typical mucinous areas stained in this way.

No "cord-like structures" (Cappell) or "nests of beakers" (Stewart) have been seen. There is no alveolar arrangement of the cells and only very few tubes, but nevertheless the cells are of frank epithelial appearance.

That the tumour is a chordoma seems certain for the following reasons: (1) Its situation within the theca growing on a pedicle as is usual with ecchordosis physaliphora; (2) The purple soft jelly-like naked-eye appearance; (3) The presence of typical physaliphorous cells and strands of cells with much mucin around them; (4) The variability in the staining reactions of the mucin.

PROGNOSIS.—Chordomata are nearly always malignant tumours, and the cellularity, nuclear variation, and hyperchromicity as shown in *Fig.* 17 *c* make it unlikely that this is an exception. On the other hand, it is still surrounded by a capsule and was growing on a long pedicle, so that the chance of complete removal is good, and only time can show what the ultimate prognosis will be.

I have been unable to find any reference in the literature to a similar case. Chordomata occasionally invade the dura mater, but this tumour not only occurred in the lumbar region, which is exceptional, but also it appeared to be entirely intrathecal.

I am greatly indebted to Dr. W. D. Newcomb for his description of the histology of the tumour, for his excellent microphotographs, and his interest and help in this case.

REFERENCES

[1] RIBBERT, H., *Centralb. f. allg. Pathol.*, 1894, v, 457.
[2] MULLER, H., *Zeits. f. rationelle Med.*, 1858, ii, 262.
[3] STEWART, M. J., and MONIN, J. E., *Jour. Pathol. and Bacteriol.*, 1926, xxix, 41.
[4] COENEN, H., Porrin's *Beitrage zur clinischen Chirurgie*, 1923, cxxxiii, 1.
[5] CAPPELL, D. F., *Jour. Pathol. and Bacteriol.*, 1928, xxxi, 797.

CARCINOID TUMOUR OF A MECKEL'S DIVERTICULUM: REPORT OF A CASE

By I. PRICE

DEPUTY MEDICAL SUPERINTENDENT, BETHNAL GREEN HOSPITAL, LONDON COUNTY COUNCIL

Tumours of a Meckel's diverticulum are extremely rare. In 1919 Symmers reported three cases of 'malignant myomata' of Meckel's diverticulum. Many cases of gastric and pancreatic heterotopia have been reported as occurring in relation to Meckel's diverticulum, but, so far as I am aware, only two other cases of carcinoid tumour of a Meckel's diverticulum have been reported in the literature. In 1922 Braxton Hicks and Kadinsky reported a case of a boy of 12 years of age who was operated on for supposed appendicitis. Laparotomy revealed a perforated Meckel's diverticulum. Braxton Hicks describes a section of his specimen as showing " in the submucosa, a strange mass of glandular tissue somewhat resembling shrunken pancreatic tissue though the arrangement is not pancreatic. This submucosal glandular tissue has an appearance of 'splendid isolation' about it, for it does not resemble any tissue in its neighbourhood and it is apparently not connected by any gland, duct or structure with the mucosa beneath which it is situated. It does not penetrate into the deeper fibromuscular structures external to it." From this description and the diagram it appears that this is a case of pancreatic heterotopia without any suggestion of neoplastic formation.

A. L. Taylor and M. J. Stewart in 1926 described a case of carcinoid tumour of a Meckel's diverticulum removed post mortem from a man aged 54 years, who was dead on admission to hospital after collapsing in the street. They found at the tip of a Meckel's diverticulum a small tumour about the size of a pea. Microscopic examination showed it to be situated in the mucosa and the submucosa. " The muscularis was broken up and penetrated by columns and masses of tumour cells and on its outer aspect the growth had slightly invaded the muscular coat. Masson's silver stain revealed argentaffin granules in the basal portions of the peripheral columnar cells."

Stewart has come to the decision that Hicks and Kadinsky's case was not a carcinoid tumour, but really a case of pancreatic heteropia, and consequently Stewart's case is apparently the first reported in the literature.

In view of the rarity of the condition it was thought to be of interest to put on record an additional case.

CASE REPORT

The patient, H. P., a married woman aged 54 years, was admitted to Bethnal Green Hospital on July 29, 1933, with a history of generalized abdominal pain since the day previous to admission. Persistent vomiting and diarrhœa had occurred. There was no history of a previous illness.

On Examination.—The patient appeared toxic. The tongue was dry and furred. Pulse 92, respiration 32, temperature 99·8°. Urine normal. The abdomen was distended

and did not move on respiration. There was diffuse tenderness over the whole of the abdomen. No mass was palpable. Rectal examination was negative. Congestion of the lung was present.

OPERATION.—Laparotomy was performed on the same day as admission after a preliminary intravenous saline infusion. Gas and oxygen were given. A right paramedian incision was made. The peritoneum was inflamed, the pelvis contained a large amount of pus, the appendix appeared normal. About 2 ft. from the ileocæcal valve, along the small intestine, the omentum was found to be adherent. On gently dissecting off the omentum, a mass about the size of a small orange was found to be attached to the bowel. At the apex of the mass was a fibrous cord about the thickness of thick silk and about 6 in. in length which was attached at its other extremity to the posterior abdominal wall just below the mesentery. The mass was found to be fairly hard, and a diagnosis of an inflamed and an obstructed Meckel's diverticulum was made. A rapid resection of the bowel was performed with side-to-side anastomosis and the pelvis was drained.

POST-OPERATIVE COURSE.—The following day the temperature settled down to normal and the pulse-rate was 98. Vomiting was absent. The bowel remained confined. On Aug. 1, 1933, the abdomen became very much distended and vomiting became a marked feature. Efforts to cause the bowels to act were unsuccessful and it was evident that paralytic ileus had supervened. Injections of anti-gas-gangrene serum and saline infusion did not produce any improvement, and on Aug. 3 the patient died.

AUTOPSY.—A limited examination was made through the incision. The small intestine was found to be much distended. The anastomosis was sound. It was evident that the cause of death was paralytic ileus.

FIG. 18.—Photograph of specimen. a, Afferent limb; b, Efferent limb; c, Diverticulum.

EXAMINATION OF SPECIMEN (*Fig.* 18).—The specimen consists of a loop of intestine, one limb measuring 6 and the other 7 cm. in length. From the junction of the two limbs there projects an appendix-like diverticulum 5 cm. long, 2 cm. in diameter proximately, and 0·6 cm. distally.

On section through the specimen, the lumen of the intestine is shown to open by a narrow orifice in each limb into a cavity about $3 \times 3 \times 2$ cm. This contains a little blood and some necrotic material. The wall of the intestine cannot be traced through the wall of the cavity, this being composed of milky white and pale yellowish tissue and measuring up to 1·5 cm. in thickness.

HISTOLOGY (*Fig.* 19).—I am indebted to Dr. W. Barnard, Histologist to the London County Council, for the microscopic description following: Sections were stained by hæmotoxylin and eosin, van Gieson, and Masson's stain. The tumour is composed of solid

trabeculæ and small acini composed of small polygonal cells separated in places by delicate strands of fibrous tissue containing blood-vessels, and in other parts by well-defined zones of fibrosis.

Similar strands and acini are present between the muscle bundles of the diverticulum. The central part of the tumour is necrosed, the cavity seen by the naked eye being necrotic

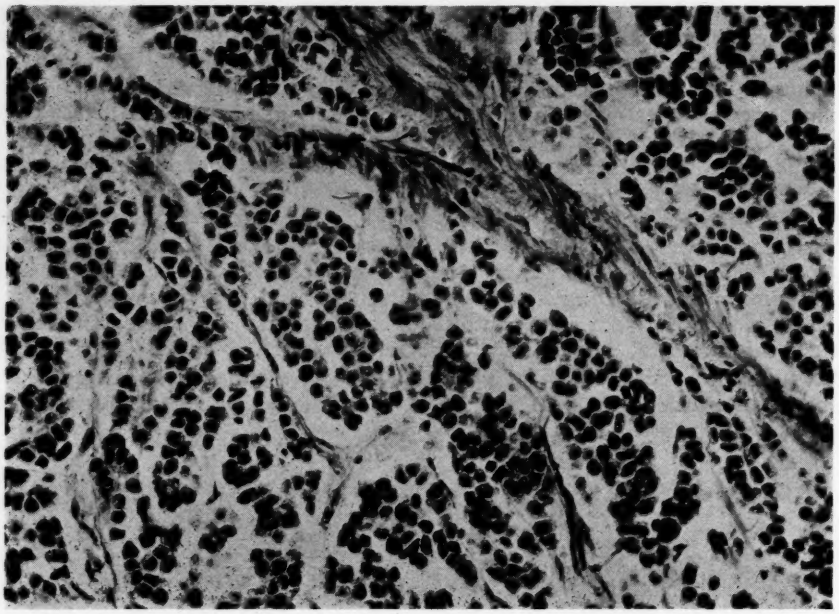


FIG. 19.—Microphotograph of section of tumour.

autolysed tumour. In no part of the sections could granules be demonstrated in the cells, and the silver stain was negative.

DIAGNOSIS.—Solid trabecular and acinar polygonal-celled carcinoid of Meckel's diverticulum.

DISCUSSION

Carcinoid tumours are most commonly found in the appendix and have in the past been confused with carcinoma of the appendix. Stewart found 17 cases in 500 consecutive appendices removed between 1910 and 1924 in Leeds General Infirmary.

In 1838 Merling described the first case of carcinoma of the appendix. The first contribution to the subject of carcinoid of the small intestine was made by Lubarsch in 1888, when he described two cases, in one of which he found two small tumours, and in the other six small tumours, in the ileum. Lubarsch described these nodules as situated in the muscularis and the submucosa and composed of nests of cells and resembling somewhat adenocarcinoma occurring elsewhere. Though the cells were dissimilar and the tumours multiple, he found no metastases. Lubarsch called them ' primary carcinoma of the ileum.'

In 1890 Random described a tumour of the ileum similar to that of Lubarsch's, but in which he found secondary deposits in the liver.

Since this time many cases have been reported, some of them being only discovered at autopsy and in cases associated with appendicitis.

A. J. Kelly described four cases and called them 'endotheliomas'. It was Obendorf in 1908 who first applied the name of 'carcinoids' in contradistinction to the carcinomas. He based his conclusion on the following facts: (1) Tumours are often multiple; (2) Cells are undifferentiated, but may show glandular forms; (3) They do not form metastases; (4) They lie in the submucosa but may send processes into mucosa; (5) Muscularis mucosa is always present; (6) Stroma is smooth muscle derived from muscularis mucosa.

Frappe considered the carcinoids to be pancreatic 'rests', while Bunting regarded them as analogous to Krompecher's basal-celled tumours of the skin.

Hubrschman in 1910 suggested that the carcinoid tumours, because of their yellow colour, were derived from the 'gelben zellen' of the intestinal mucosa. Schmidt had previously established the chromaffin character of the 'gelben zellen'.

Gosset and Masson in 1910 applied the silver impregnation method of staining the chromaffin cells, and described them as: (1) Occurring in the depths of the crypts of Lieberkühn throughout the gastro-intestinal tract; (2) Occurring between the cells of the mucosa, some extending to the lumen and others not; (3) Showing argentaffin or silver staining granules in the cells; (4) Cells showing vacuoles in cytoplasm which are probably the results of elaboration of granules.

Gossett and Masson proceeded further, and they showed that the carcinoid tumour cells closely resemble and are identical with the chromaffin tissue of paraganglia which are filled with argentaffin granules. Masson regarded them as endocrine tumours because the medullary cells of the suprarenal exhibited microchemical similarities. Masson's researches have progressed still further, and in 1928 he showed in chronic cases of appendicitis the argentaffin cells derived from the Kulchitsky cells situated amidst the cells of the crypts of Lieberkühn had invaded the hyperplastic nerve plexus or musculo-nervous complex and that further development resulted in the formation of a carcinoid tumour.

Summary of Theories Concerning the Carcinoids.—The theories concerning the carcinoids may be summarized as follows: (1) They are carcinomas; (2) They are basalomas analogous to Krompecher's basal-cell tumours of the skin; (3) They are pancreatic rests. (4) They are chromaffinomas derived from the Kulchitsky cells of the crypts of Lieberkühn and therefore are tumours of the paraganglia.

Discussion on the Case Reported.—It will be noticed that the case reported does not stain with Masson's stain. On the other hand, it does not appear that the section is that of a pancreatic rest. It has not the appearance of 'splendid isolation' that we see in cases of pancreatic rest, and, further, the cells are definitely invasive in character. We can therefore assume, perhaps with reservation, that the cells may be more primitive in type than those of the fully developed carcinoid

SUMMARY

1. A short review of the literature on carcinoids is given.

2. The rarity of a carcinoid in Meckel's diverticulum is emphasized.

3. A case of tumour of a Meckel's diverticulum is reported, and it is suggested that the cells are of a primitive carcinoid type.

4. The pathology of the carcinoids is reviewed.

I wish to make grateful acknowledgement to Dr. W. G. Barnard, Histologist to the London County Council, for sections, photographs, and pathological descriptions; to Professor M. J. Stewart, of Leeds, for his criticism; and to Dr. Braxton Hicks for his kind help.

BIBLIOGRAPHY

EWING, *Neoplastic Diseases.*
SYMMERS, *Ann. of Surg.*, 1919.
LUBARSCH, *Virchow's Arch.*, iii, 280.
KROMPECHER, *Beitr. z. pathol. Anat.*, 1919.
FORBES, "Tumours of the Appendix and Small Intestine", *Bull. Johns Hopkins Hosp.*, 1925, xxx, 130.
MASSON, "Carcinoids and Nerve Hyperplasia of the Appendicular Mucosa", *Amer. Jour. Pathol.*, 1928, iv, 151.
MASSON, "Contribution to the Study of the Sympathetic Nerves of the Appendix. The Musculo-nervous Complex of the Submucosa", *Ibid.*, 1930, vi, 217.
BRAXTON HICKS and KADINSKY, "Carcinoid Tumour of a Meckel's Diverticulum", *Lancet*, 1922, ii, 70.
STEWART and TAYLOR, "Carcinoid Tumour of Meckel's Diverticulum", *Jour. Pathol. and Bacteriol.*, 1926, xxix, 135.

INCISIONAL HERNIA*

By E. S. J. KING
SURGEON TO OUT-PATIENTS, MELBOURNE HOSPITAL

MANY 'causes' of incisional hernia are given in text-books and current papers. Some of these—for example, the presence of infection, the use of drainage tubes, "too early adoption of the upright posture", etc.—do not deal with a fundamental factor, and others ("inadequate formation of the cicatrix", "giving way of the scar", etc.) are but imperfect statements of one or other of the phenomena which are associated with and not causative in the development of the condition.

An attempt has been made here to show that the many factors which are regarded as causative may be reduced to terms of certain fundamental principles.

HISTORICAL

During the Middle Ages the various forms of abdominal hernia were not differentiated from each other. In 1585 Guido de Chauliac in his *Chirurgica Magna* distinguished umbilical hernia from those occurring in other parts of the abdominal wall. Further observations were made, amongst others, by La Chausse in his *Dissertation de Hernia Ventralis* in 1746, and by Klinkosch in 1764.

It was only at the beginning of the last century, however, that attention was attracted generally to the ventral herniæ. A ventral hernia was described as a protrusion "through an unnatural opening in the front or side of the belly". At this time the majority of ventral herniæ were those through the linea alba and the linea semilunaris. A few cases following wounds by knives, sabres, bullets, etc., were encountered. In Chelius' *System of Surgery*, translated by South in 1847, it was stated that ventral hernia "is much more rare" than umbilical hernia. At this time post-operative rupture is not mentioned.

As abdominal section became more common it was found that herniæ through the scars were occurring in considerable numbers. In 1893, in his *Treatise on Ruptures*, Jonathan Macready remarked, "It is not now uncommon to find a traumatic hernia after the operation for Ovariotomy".

Despite improvements in technique, in asepsis, in anæsthesia, and post-operative treatment, hernia after operation still remains a serious problem.

CLINICAL CHARACTERISTICS

Incisional hernia is here referred to as the protrusion which occurs through the site of a wound, and is not intended to include those cases in which a bulging

---

* Since writing the above I have observed an account of the development of incisional hernia (Freeman, L., "Cause of Post-operative Rupture of Abdominal Incisions", *Arch. of Surg.*, 1927, Feb., 600) which contains a consideration of the problem from a somewhat different aspect. On the fundamental point, however, there is agreement.

occurs as the result of loss of tone or degeneration of muscle following injury to nerves. It arises through any of the incisions which are made in the abdominal wall—most frequently in the lower portion of the abdomen. In 150 consecutive cases it was found that post-operative hernia occurred through a sub-umbilical mid-line incision in 30 per cent of cases, muscle-splitting (McBurney) incision in 27 per cent, sub-umbilical paramedian incision in 14 per cent, and supra-umbilical paramedian incision in 14 per cent. There is usually a latent period between the time of operation and the development of the hernia. This may be very short, only two or three weeks, or several years may elapse before the observation of a pulsatile swelling under the scar.

Table I.—Interval Between Operation and Development of Hernia in 150 Cases

Time between Operation and Development of the Hernia	Number of Cases	Percentage
0–4 weeks	61	40⅔
1–3 months	15	10
3–6 months ..	19	12⅔
6–12 months ..	18	12
1–2 years	12	8
2–5 years	7	4⅔
5–10 years	6	4
10–20 years	3	2
Over 20 years ..	1	⅔
Not given	8	5⅓

It will be seen from *Table I* that the majority of the cases were observed shortly after the operation, usually when the patient was allowed out of bed. This observation may be the reason for the opinion that too early assumption of the erect attitude is responsible for the development of such herniæ. When allowance is made for the obesity of many of the patients—which makes early observation difficult—and also for the fact that in many cases the first observations are made by the patients themselves, so that any abnormality of mild degree is probably overlooked for some time, it is apparent that the great majority of the cases occur almost immediately after the operation.

As shown in *Table I*, 40 per cent of the herniæ develop within a month of operation, i.e., they are present when the patient gets out of bed; 50 per cent are present within three months, 63 per cent within six months, and 75 per cent have become obvious within a year. On several occasions I have examined a scar and discovered a hernia of which the patient was quite unconscious, so that most of these periods should probably be shortened in order to gain a real idea of the time of development of the condition. Incidentally in some cases the patients had 'no idea' of the length of time that the hernia had been present (last group).

Some of the cases seem almost certainly to be late developments and due to a tearing of the peritoneum at a late stage; e.g., in the case in which the hernia developed over twenty years after the operation (twenty-six years), the patient noticed a swelling after a severe abdominal strain associated with pain in the scar. Three other cases, with 8-year, 12-year, and 15-year intervals, all experienced injuries or strains which gave rise to pain in the wound. Several of the cases

occurred during the late stages of pregnancy or parturition; one who showed a 5-year interval gave birth to twins just before noticing the hernia.

It is almost impossible to decide in these cases whether there is actually a tearing of the scar tissue or whether there had been a latent hiatus in the scar (filled with omentum) all the time. Inasmuch as on the one hand the latter may remain latent, and on the other scar tissue is very firm and strong, the second hypothesis seems more likely even for the late cases. The increased intra-abdominal pressure therefore causes a rapid increase in size in the original small herniation.

When the hernia is first observed it is often a typical protrusion of intra-abdominal contents through the wall, more or less reducible, and giving a definite impulse on coughing or straining. When observed at an early stage of its development, however, it may not be reducible or show an impulse on coughing. It may be mistaken for a small hæmatoma, more or less organized. Later it develops the characteristic features of the well-developed condition.

The hernia, if allowed to develop without interference, gradually becomes larger and larger; some very large examples may be encountered, but this is unusual, since the life history is cut short by obstruction of the gut.

The neck of the sac is often found to be relatively small, and often there is more than one opening through the abdominal wall.

SURGICAL ANATOMY

The hernia is usually irregularly ovoid or rounded in shape, showing a number of loculations. It is covered by a layer of fibrous tissue, fat, and skin. Sometimes

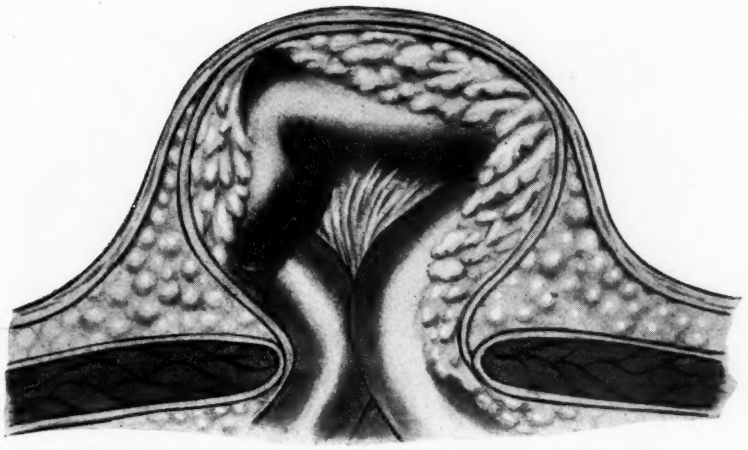


FIG. 20.—Diagrammatic representation of an incisional hernia which contains small bowel and omentum.

the cavity comes into close proximity with the skin, and the sac may be adherent to it.

The neck is a firm fibrous ring, which is usually much smaller than would be expected from a clinical examination of the hernia before operation. If the hernia is reducible, even partially, the dimensions of the neck may, of course, be determined before operation.

The septa separating the loculi in the sac project for varying distances into the cavity (*see Fig.* 21), and some may extend so far as to divide the opening at

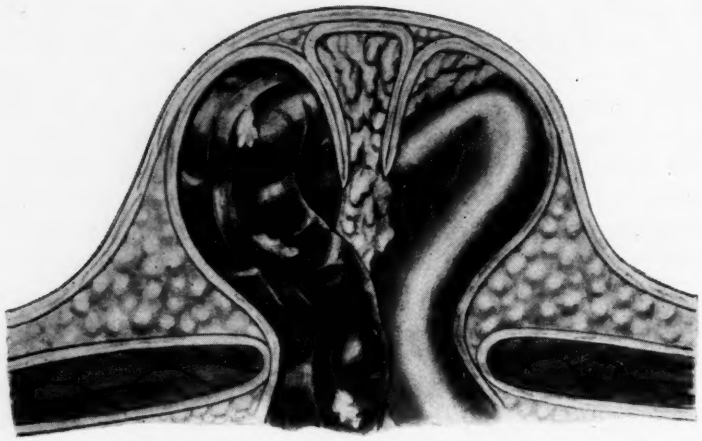


FIG. 21.—Diagrammatic representation of an incisional hernia which contains large intestine, omentum, and small intestine. Septa which partially subdivide the hernial sac are shown.

the neck, i.e., the neck consists of more than one opening into the sac. The sac is lined by a serous layer which is thinner and more tenuous in appearance than normal peritoneum.

The contents of the sac may be omentum only or omentum and bowel, either small or large intestine or both (*Figs.* 20, 21). The contents, particularly

FIG. 22.—Drawing of the peritoneal aspect of scar tissue removed from the site of an old operation. Multiple openings which had contained omentum are shown. These strongly suggest the escape of omentum between sutures.

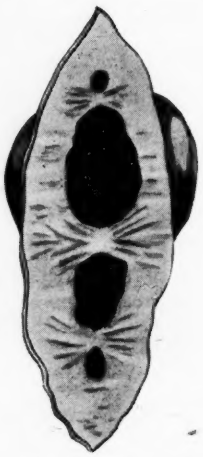


FIG. 23.—Drawing of the peritoneal aspect of tissue removed in a case of incisional hernia. In addition to the large opening (sac shown behind) there are other smaller openings (cf. *Fig.* 22).

the omentum, are usually adherent at various places to the wall of the sac. These 'adhesions' are slight and tenuous in some cases, but are often dense and thick,

containing dense fibrous tissue. The 'adhesions' are significant from the point of view of the mode of development of the hernia, and are discussed again.

In some cases there are separate openings in the scar for a number of small distinct herniæ. These may be well demonstrated at times when the scar tissue has been removed completely. This is shown in *Figs.* 22, 23.

HYPOTHESES OF THE MODE OF FORMATION OF INCISIONAL HERNIA

A number of different factors are regarded as being causative. Some of these —use of a drainage tube, suppuration, or raised intra-abdominal pressure—are, or have been, present, but do not supply the explanation of the mode of formation. " Inadequate formation of the cicatrix ", " giving way of the scar ", " poor healing " are only indefinite statements of opinion—statements without any basis of direct observation for their support. " The too early adoption of the upright posture " is even more nebulous, since this involves a number of fundamental conditions such as alterations of intra-abdominal pressure, the mechanism and rate of healing, etc. From my own experience I would regard it as playing but little part in the development of hernia. " Imperfect technique " is undoubtedly the cause of many cases, but a statement of exactly where the technique is unsatisfactory is necessary.

A number of observations on early cases, the multiple loculations, the frequency of adhesions, the difference in the appearance of the lining of the sac of the hernia from ordinary peritoneum, all suggested that the sac did not arise by the pulsion of peritoneum through a weak area of the wound by the pressure of the intra-abdominal contents. The observations were then reviewed in the light of the hypothesis that the sac is secondarily formed. Animal experiments were undertaken.

Experimental Material.—Cats were taken and ventral herniæ produced. A mid-line incision into the abdominal cavity was made under general anæsthesia, and the skin then separated from the obliquus abdominis externus for a considerable distance laterally. A small opening was made in the abdominal wall in the lateral part, and omentum was passed through into the subcutaneous tissues. One part of it was tethered by a catgut suture. In some cases a loop of small intestine was also passed through the opening and tethered. (Plain oo catgut was used.) The mid-line wound was then closed in layers. Except for one cat in which suppuration occurred in the wound, and two others in which intestinal obstruction in the hernia supervened before the sixth day, the animals made an uninterrupted recovery.

At first a firm mass could be felt in the region of the prolapsed omentum. There was no impulse when the animal struggled. The wounds healed and the condition of the swelling remained stationary until at a variable time later (seven days in one cat, fourteen days in another, but on an average about ten days) the mass was found to show an impulse when the animal struggled. This gradually became more obvious until there was a typical hernia. One hernia became smaller in size and finally almost reduced itself completely, only a small amount of additional tissue being felt in the subcutaneous layer. Two others became much larger, but the majority remained about the same size.*

---

* This is possibly to be correlated with the relative infrequency of herniæ in quadrupeds. Also the animals were observed only for quite short periods.

The animals were sacrificed at different times after the operation (five to twenty-eight days). The anterior abdominal wall containing the hernia was removed and the omentum and gut (where present) passing into the hernia were cut at a distance from the abdominal wall. The hernia was then dissected.

In the early examples (five to ten days) the omentum and bowel were found to be adherent to the surrounding connective tissue. This could be separated readily by sharp dissection or by a blunt instrument with tearing of the adhesions. No cavity could be found round the omentum. In the later cases, and usually in those in which pulsation had been present when the animal struggled, small cavities separating the omentum or bowel from the connective tissue could be found (i.e., small serous spaces). These were best developed in those examples which were investigated the longest time after operation (*Fig.* 24).

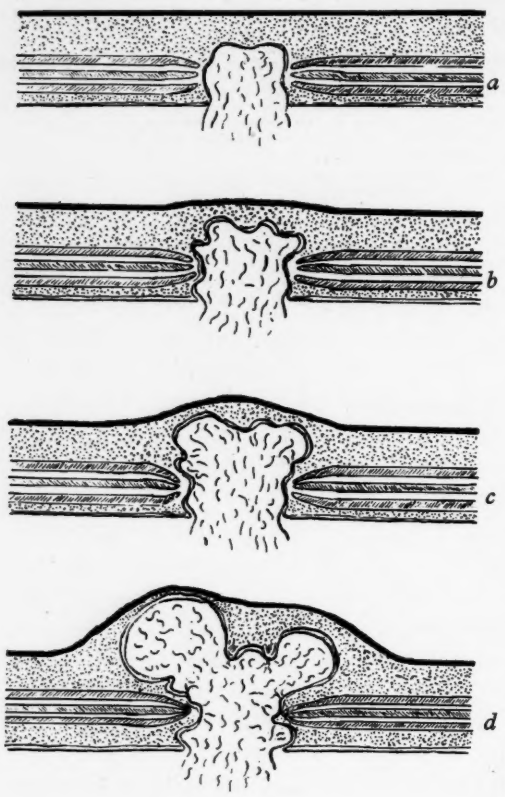


FIG. 24.—Diagrammatic representation of the mode of development of the sac of an incisional hernia. *a*, Prolapsed omentum; *b*, Small serosal cavities forming in part from the serosa of the omentum and in part by ingrowth from the peritoneum; *c*, Further stage of *b*; *d*, Enlargement of the hernia and coalescing of adjacent serosal spaces.

FIG. 25.—Photograph of specimen of a hernia, viewed from peritoneal aspect, showing omentum entering the sac (sixteen days). The neck is well demarcated.

The cavities were small and separated from each other by bands or areas where the hernial contents and the wall were still adherent. In some examples the cavities were near the entrance to the abdomen and appeared to communicate with the abdominal cavity. The neck of the hernia was usually well marked (*Fig.* 25).

The demonstration of the independence of some of the serous cavities from each other and the continuity of some with the peritoneum was performed as follows: Herniæ were produced (as above), and after five to six weeks, under anæsthesia, a solution of methylene blue was injected into the abdominal cavity. This was massaged into the region of the hernia. The hernia was now examined after removal of the skin over it, from the superficial aspect. Some of the loculi of the sac were obviously distended with the blue fluid, while others were found on dissection not to be stained. Comparable uninvolved loculi were injected with carmine gelatine and it could be seen that (1) they did not communicate with the 'blue' loculi, and (2) they did not all communicate with each other. Some difficulty was encountered in placing the injection within the serous cavities, but by trial and error (injection was sometimes commenced into tissue planes, but this was early recognizable and proved later on dissection) injection of a number of cavities was made (*Fig.* 26). However, even without this the freedom of certain

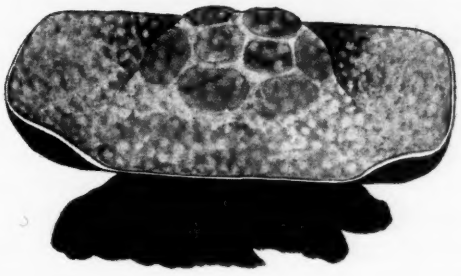


FIG. 26.—Drawing showing the loculi of a hernia filled with dye. The peritoneal surface and intraperitoneal contents are stained blue, and some of the loculi in the sac are blue. Other loculi are stained with carmine.

loculi from the blue coloration in the first experiment seems to be a satisfactory demonstration of their separation. This was controlled by attempting to force the carmine into the abdominal cavity. This was achieved with ease by injecting a 'blue' loculus, but could not be performed even by bursting other loculi. Two deductions may be drawn from this:—

1. Since certain of the loculi are formed away from the peritoneal lining near the neck of the sac, and are not in communication with it, the endothelium (or mesothelium) lining such loculi must have arisen from multiplication of the serosa of the omentum or bowel. After this multiplication, splitting of the cellular (mesothelial) tissue probably occurs so that each side now possesses a lining. Attempts were made to demonstrate this histologically, but a completely convincing picture was not obtained.

2. The fibrous bands or areas which separate the various loculi are, on dissection, closely similar to the 'adhesions' found at operation.

Since within the limits of these experiments these adhesions become fewer in number and less well marked as the condition progresses, it is assumed that they are the residue after partial 'peritonealization' of the hernia. It is possible that the sac is at first formed and then secondary adhesions arise, but no evidence of inflammation of the bowel was to be seen. Almost certainly such inflammatory and secondary adhesions occur in human beings, but at least in the early stages the method of formation of the 'adhesions' described above seems probable.

In some cases either the various loculi become continuous with each other or all the serosal lining is developed from one origin (possibly the peritoneum), because rarely the whole sac may be free from ' adhesions ' and the contents lying free within it. This was found in one cat, in which the hernia was examined at the end of a month.

DISCUSSION

As with so many other conditions encountered in surgical practice, the incisional hernia is most commonly observed in a well-developed form which is actually the end-result of changes the nature of which can only be conjectured. The evidence nevertheless, though only circumstantial, seems to point in a definite direction.

The anatomical features of the developed hernia, particularly the relatively large size of the sac in many cases as compared with the opening in the wall, indicate that the factors are definitely localized to one point in the wound. Thus a " giving way " or " stretching " of the scar does not explain these cases. In the examples where there are multiple openings (*see Figs.* 22, 23) the same argument applies, since these openings are quite distinct from each other and separated by bands or sheets of ordinary scar tissue—i.e., the factors are still acting locally, though in more than one place.

The problem is: What factors cause or allow the local protrusion of the abdominal viscera? Omentum or even bowel will pass very readily into any small hiatus which is left between sutures. On one occasion, three days after operation, a small knuckle of bowel was found in the tissues of the anterior abdominal wall. The cause appeared to be the cutting, or at least the laceration, of the catgut peritoneal suture by the cutting-edged needle on which the silkworm-gut sutures were threaded. In another case a small piece of omentum had prolapsed through the small opening made by the passage of a bullet (*Fig.* 27).

The difficulty in preventing a small piece of omentum from entering the wound when this is being sutured, particularly when anæsthesia is difficult or incomplete, is shown by the many methods suggested for preventing this. Careful observation of operations at this stage, incidentally when most onlookers cease to take interest, shows that small pieces or tags of omentum are sometimes included in the wound between sutures. This suggested the experimental work undertaken, and the similarity of the clinical course of the experimentally produced herniæ with some post-operative ones suggests that this is the actual mode of formation.

The observation that so many of the cases have a hernia when they are allowed out of bed also strongly suggests that some such mechanism of formation occurs. If this is so, then at least some of the cases are due to error of technique—i.e., intra-abdominal contents, usually omentum, are allowed to escape into the extra-peritoneal tissues.

Others, however, do not fall into this class. The commonest cause of hernia is infection. The mode of development here is associated with early solution of portion of the catgut and the delayed healing of the wound. This may be readily observed in those cases when it is necessary to re-open the wound two to four days after the operation. This disappearance of the catgut prematurely gives a condition of affairs similar to that seen in the previous group of cases. Some degree of intestinal distension is often present and a small amount of omentum or bowel passes into the wound.

Debilitating conditions—e.g., carcinoma—are recognized as delaying healing. I have seen, after the removal of sutures in such a case, the wound open as late as the twenty-first day. The solution of the catgut before healing has occurred will allow the passage of omentum into the wound. This, therefore, also may be correlated with the first group. Such cases are closely related to those of "disruption of an abdominal wound" or "burst abdomen", the difference between these and a hernia being largely a question of degree of protrusion of the viscera into or through the abdominal wall.

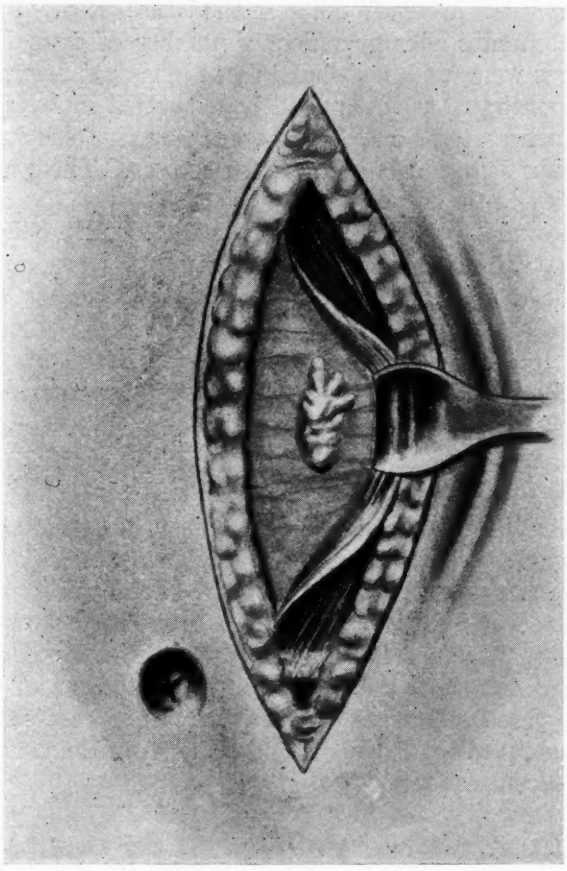


FIG. 27.—Drawing of an abdominal wound (left upper paramedian) showing the prolapse of a piece of omentum through a bullet hole. The bullet wound had occurred two hours before operation.

Raised intra-abdominal tension is, of course, a factor in the production of hernia in so far as it will facilitate the protrusion of omentum or bowel, but its importance is secondary to the integrity of the suture line.

The adoption of the upright posture does not seem to me to be a primary factor in the development of the condition, which depends on the presence of a hiatus in the wound.

Once the condition has commenced, omentum having entered the wound, formation of the sac will occur, and this will then gradually become larger. The

early development of a non-pulsatile swelling which later becomes pulsatile, as mentioned above and observed in the animals, strongly supports this mode of formation.

From a consideration of the above, certain principles of technique appear. These are more or less generally recognized, but emphasis may not be out of place. No hiatus must be left in the suture line, and no tissue—particularly omentum—even in the smallest amount, must be allowed between sutures. Through-and-through sutures, if closely placed and no omentum prolapses between them, will give a satisfactory wound which will not be followed by hernia in any greater proportion than in those in which other methods are used. I have had occasion to re-open, several months after operation, a number of cases in which through-and-through sutures were used, and found that the various layers of the abdominal wall could be demonstrated as if they had been sutured in layers. Small tears in the peritoneum such as sometimes occur when there is some straining of the wall are just as dangerous as openings between the sutures. These may be avoided by the use of through-and-through sutures.

Drainage tubes and wound infection present difficult problems. Having seen herniæ develop in two of my earlier cases through a muscle-splitting incision, I have since made it a practice to bring the tube through a stab incision, thus allowing complete closure of the wound. Where infection of the wound is probable —e.g., in an appendiceal abscess—swabbing the wound with sterile vaseline or bipp before opening the peritoneum greatly diminishes the incidence of wound infection.

CONCLUSIONS

The essential feature in the development of an incisional hernia is the escape of some of the contents of the abdomen (usually a small piece of omentum). This may occur through a small tear in the peritoneum or through a small hiatus between sutures. In the case of infection, the early solution of the catgut may allow the escape of omentum. The sac is formed secondarily round such tissue and may then become larger and show the characteristic phenomena of a pulsatile hernia. The adhesions so frequently found in these herniæ are not secondary adhesions, but are due most frequently to the localized rather than the completely generalized formation of the secondary sac.

The experimental work was performed in the Department of Pathology, University of Melbourne, and I am deeply indebted to Professor P. MacCallum for his encouragement, criticisms, and suggestions. My thanks are due to Dr. E. Ford for assistance with the examination of case histories and to Dr. I. C. MacDonald for help with the animal experiments.

POSTERIOR SEGMENTAL BLOCK-EXCISION OF THE BLADDER NECK WITH PRIMARY CLOSURE

By S. HARRY HARRIS

HONORARY UROLOGIST, LEWISHAM HOSPITAL, SYDNEY

THE operation of posterior segmental block-excision of the bladder neck with primary closure is presented in the belief that it is an improvement on the well-recognized operations of cuneiform (or wedge) resection and of complete extirpation of the bladder neck ("*ablation totale du col*" of Marion). The first-named operation is too liable to be followed by recurrence of the obstruction. The latter operation, while yielding apparently excellent results according to the reports of its sponsors, is open to the objections that it is needlessly extensive and that it leaves a wide-open raw surface, the bleeding from which is controlled by gauze packing (Marion[1]).

The operation devised by the author, and herewith described, has been practised by him thirty-three times in the past six years without mortality and, up to the present, without recurrence of obstruction. It may be regarded as a companion to the author's operation of suprapubic prostatectomy with closure.

The operation is designed for the relief of certain obstructive conditions of the bladder neck when no gross enlargement of the prostate is present, the "*prostatisme sans prostate*" of the French. These conditions include the various types of median bar formation or disease of the posterior commissure and general prostatic fibrosis. The operation has no place in the treatment of lateral lobe enlargement of the prostate, though it will prove of value in some cases where the bladder has to be opened for the treatment of recurrence of obstruction after prostatectomy.

The tissue removed at operation may prove to be fibrous, adenomatous, or muscular, alone or in various combinations, or occasionally even carcinomatous.

The operation is undertaken only after definite proof is forthcoming that there is present no adenomatous tissue in the prostatic rim which is capable of digital enucleation. To ensure this a careful bimanual palpation is carried out with the forefinger of one hand placed in the previously dilated prostatic urethra, and the forefinger of the other in the rectum. To remove an obstructing posterior lip and to leave behind adenomatous tissue elsewhere in the prostate is merely to court future trouble. This, of course, constitutes an essential weakness in the per-urethral methods of operation.

Per-urethral resection will, however, still be the method of choice in dealing with some forms of obstruction of the bladder neck when no gross enlargement of the prostate is present; in others the trans-vesical approach will be considered preferable. In making the selection due regard must be paid not only to the actual obstructive condition of the bladder neck, but also to the presence of possible complications such as calculus or diverticulum of the bladder, gross hypertrophy

of the inter-ureteric bar, and the like. The author's experience during the past six years is about evenly divided between the two methods. He is at present decidedly of the opinion that in the long run the trans-vesical operation herewith described will more than hold its own with the per-urethral methods of resection both as regards immediate safety and, more particularly, for permanence of results. In either case the pre-operative treatment will be the same as for prostatectomy.

OPERATIVE TECHNIQUE

After exposure of the bladder base by the same technique as the author employs for prostatectomy, the tip of the right forefinger is gradually but firmly insinuated through the internal meatus. The very dense, infiltrated bladder neck with contracted meatus, so often present in the type of case under review (*Fig.* 28), not uncommonly declines to yield to any but the firmest and most persistent pressure. Two fingers of the left hand are passed into the rectum and provide an invaluable point of counter-pressure during this manœuvre. This preliminary dilatation is very important and greatly simplifies the subsequent steps of the operation.

FIG. 28.—Showing the indurated contracted meatus often found in disease of the bladder neck, and hypertrophy of the inter-ureteric bar.

Two deep traction sutures are now placed in position, one on each side about half-way round the dilated prostatic rim (*Fig.* 29). Following this, at least $\frac{3}{4}$ in. of the hindmost sector is excised (*Figs.* 30–32). In order to carry out this excision two deep parallel vertical incisions are made, one on each side of the mid-line and reaching in the depths down to the level of the floor of the prostatic urethra (*Fig.* 30). The intervening lip is then firmly drawn up by traction forceps and cut out deeply and cleanly in a transverse direction by sharp scissors (*Fig.* 31). The bared base (*Fig.* 32) must be carefully reviewed, and, if need be, trimmed up. It is important that no gross fibrous or adenomatous remnants be left in

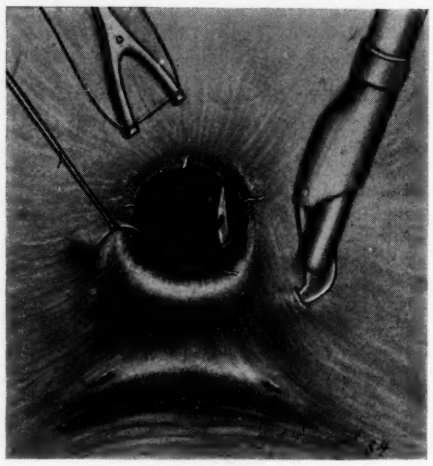


FIG. 29.—The same case as *Fig.* 28, after digital dilatation of the meatus. The left lateral traction suture is in position. The boomerang-needle is ready to receive the right lateral suture from the ligature carrier. The ready access afforded by the preliminary dilatation is well shown. The slight lacerations resulting from the dilatation are indicated.

this situation. The cross-cut ends of the prostatic rim are next freely undercut on each side to permit of their complete retraction (*Fig.* 33 and inset). Two deep hæmostatic sutures are then passed on each side behind the two traction sutures that were inserted prior to the excision. These sutures also serve to

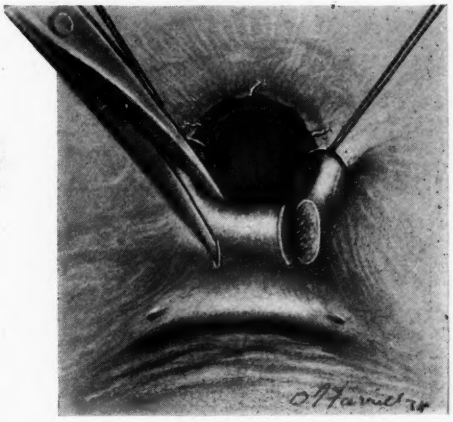


FIG. 30.—The traction sutures in position: the deep vertical incision of the bladder neck completed on the right—scissors shown beginning the left.

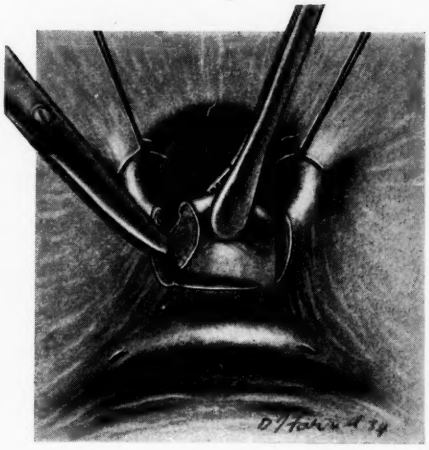


FIG. 31.—Vertical incisions complete. Block-excision in progress.

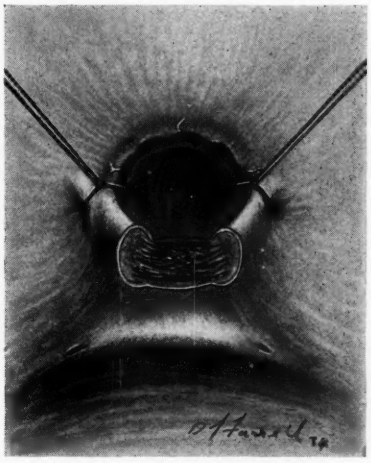


FIG. 32.—Block-excision completed, showing fibrous bands running from the cross-cut ends to the floor. These are a potential source of recontraction when left behind.

turn in on each side the bared face, of the cross-cut ends, thus eliminating the raw surface in this situation (*Figs.* 34–36). If necessary one or more additional sutures are placed to ensure complete hæmostasis. When hæmostasis has been accomplished, retrigonization is carried out. This step, which the author first

described in the operation of suprapubic prostatectomy with closure, is of equal value here. Retrigonization is the name which the author has applied to the method of sewing down the apex of the trigone into the prostatic urethra, its normal habitat, in order to ensure freedom from post-operative ledge formation

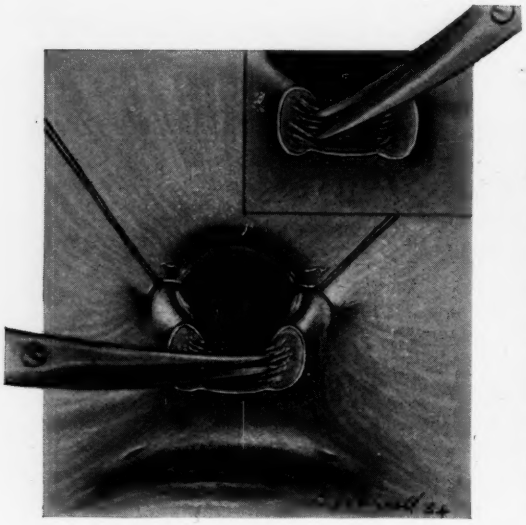


FIG. 33.—Undercutting of the cross-cut edges.

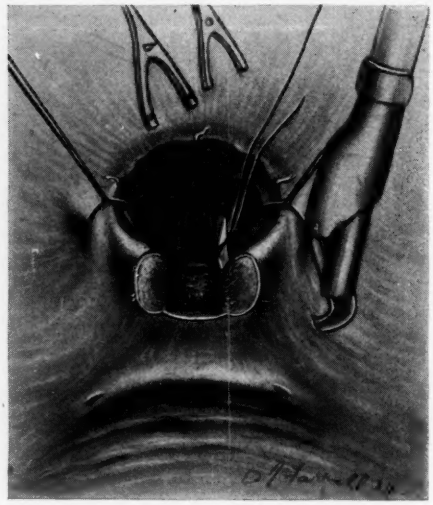


FIG. 34.—Insertion of first hæmostatic suture on the right behind the original traction suture.

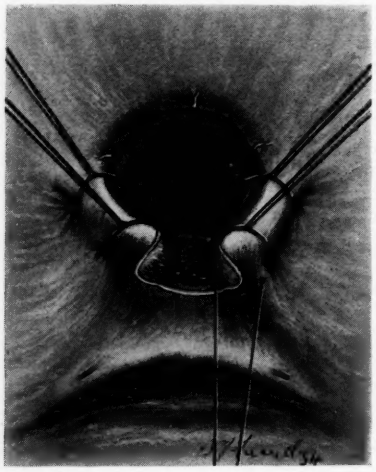


FIG. 35.—First right and left hæmostatic sutures tied, second right lateral hæmostatic suture in position before tying. The tying of this suture turns in the cross-cut edges and obliterates the raw surface in this situation.

after prostatectomy (Harris[2]). The point of the needle for this step (*Fig.* 36) penetrates the bladder base at the deepest part behind the inter-ureteric bar, following the author's latest practice (Harris[2]).

Retrigonization completes the plastic portion of the operation (*Fig.* 37). The anterior obliterative sutures which are employed after suprapubic prostatectomy are not required for this operation, as the anterior segment of the bladder neck has not been interfered with and there is no raw surface left to obliterate.

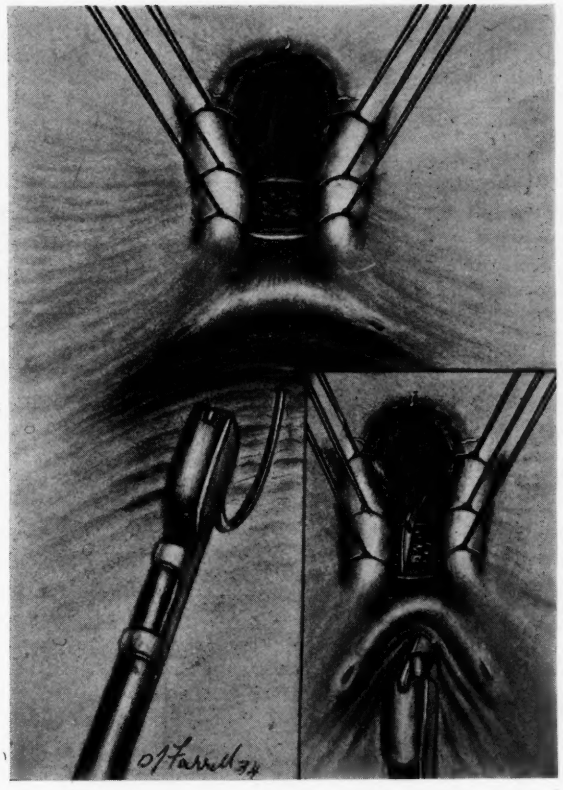


FIG. 36.—Lateral sutures in position, hæmostasis complete. Retrigonization begun: the point of the boomerang-needle is about to penetrate the deepest part of the bladder base well down behind the trigone. *Inset*: The point of the needle emerging in the prostatic urethra ready to receive the suture.

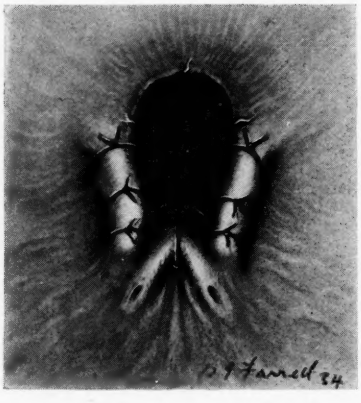


FIG. 37.—Retrigonization complete: the apex of the trigone sewn well down into the prostatic urethra. All raw surfaces obliterated.

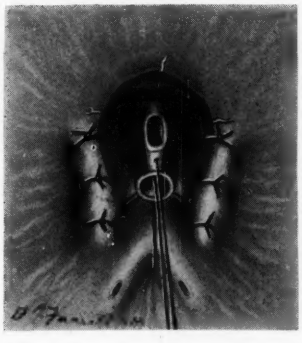


FIG. 38.—Catheter in position ready for complete closure of the bladder.

A number 22 French rubber catheter is passed through the urethra into the bladder, and its end, including the eye, is cut off after an opening has been cut about an inch behind the eye. The catheter is suspended in position by a silkworm gut suture (*Fig.* 38). The bladder and abdominal wounds are completely closed and the silkworm gut suture is suspended to a small glass rod on the abdomen according to the author's practice after prostatectomy.

The after-treatment is the same as that employed after prostatectomy.

SUMMARY

1. A new operation is described for the treatment of obstructive disease of the bladder neck in which there is no gross enlargement of the prostate. It may be regarded as a companion to the author's operation of suprapubic prostatectomy with closure. It has been carried out thirty-three times without mortality.

2. The operation described eliminates the liability to recurrence of obstruction which characterizes cuneiform resection.

3. The operation is less extensive and safer than complete extirpation of the bladder neck ("*ablation totale du col*" of Marion) and should ensure results at least comparable with those claimed for this operation.

4. The diseases for the treatment of which this operation has been designed will often be treated by per-urethral resection, though with what degree of permanence yet remains to be proved.

5. The type of operation selected should be determined not only by the particular local obstructive condition of the bladder neck but also by the incidence of such complications as stone and diverticulum of the bladder.

REFERENCES

[1] MARION, G., "Maladie du Col vesical", *Trans. Fifth Congress Internat. Soc. of Urol.*, 1933, July 11–15, 393.

[2] HARRIS, S. HARRY, "Suprapubic Prostatectomy with Closure", "*Austral. and N.Z. Jour. Surg.*, 1935, Jan., 226.

A CASE OF HYPERINSULINISM RELIEVED BY PARTIAL PANCREATECTOMY

By J. ALLAN BERRY

HONORARY SURGEON, NAPIER HOSPITAL, NEW ZEALAND

SINCE the clinical picture of insulin shock from overdosage (hyperinsulinism) has become generally known, some hundreds of cases of spontaneous hypoglycæmia have been reported in the literature. The condition is associated with a variety of clinical syndromes and there can be very little doubt that when the less severe cases of the malady become generally recognized it will be found to be a relatively common complaint. Those cases caused by an adenoma of the pancreas have lent themselves to surgical treatment with excellent results, but those cases where the pancreas appeared normal and where partial pancreatectomy has been carried out have, up to the present, been unsatisfactory. Wauchope[1] states that "Partial resection of a normal pancreas does not seem worth while." The opposite view is held by Wilder,[2] who made the confident prophecy: "The situation is analogous to that of the early history of surgery in hyperthyroidism. The results in this new field ought to be as good as those obtained in hyperthyroidism, and I predict they will be." Best,[3] on the other hand, states, "While it is possible, as has been suggested, that a small tumour might escape attention, it is by no means clear that the history of the development of the surgical treatment of hyperthyroidism will be repeated in this instance." After mentioning the rational treatment of these cases (1) by supplying carbohydrates, (2) by stimulating new production of carbohydrates as by thyroxine, (3) by the surgical removal of a tumour should it be present, he states, "To this list there may shortly be added the use of a potent diabetogenic substance prepared from the anterior pituitary. If, as may well be the case, the therapeutic effects of the extract from the anterior lobe are not satisfactory, the clinician will probably be forced in severe cases of spontaneous hypoglycæmia to recommend excision of a large part of the pancreas, irrespective of whether or not the presence of an adenoma is suspected."

The object in reporting the following case is to show that when a sufficient amount of normal pancreas is removed, alterations take place in the blood-sugar which persist for some months, and the condition of hyperinsulinism may be relieved.

CASE REPORT

Miss A. M., a school teacher, aged 58 years, was first seen on Dec. 8, 1933, following a hypoglycæmic attack.

HISTORY.—The patient's father died from "natural causes" at the age of 89 years, and her mother of "peritonitis" at the age of 86 years. There was no family history of diabetes or glycosuria. Two sisters suffer from attacks that may be due to spontaneous hypoglycæmia.

At the age of 11 years she had a severe attack of measles and at the age of 12 mild diphtheria. Apart from symptoms referable to the present condition, she had suffered from no other

illness except from what was diagnosed as rheumatic fever ten years ago, when she was off duty for five months. The menopause had occurred at 51 years and was symptomless.

The first attack of vertigo, which was her outstanding complaint, came on suddenly about fourteen years ago while in a cinema. Next morning on waking she was still a little dizzy. Some time later another attack of dizziness occurred, when she vomited freely. Shortly after this, in her own words :—

" I was awakened at about 4 a.m. daily and would find my hands resting on my stomach, and on removing them, this awful depressing feeling of being thoroughly ill would pass off and then I would vomit quietly as if the stomach revolted from food. I would sleep then, till time to arise. My breakfast consisted of a cup of tea and a granose biscuit. Sometimes I was not too steady on my walk of nearly two miles to school. This gradually increased until I became very unsteady in my gait and often used to stagger in places and had to keep my eyes 'front', not daring to look sideways. Then came dizzy turns at school, where I would sit quietly for half an hour or so and then go out and vomit. This would give relief, and I would then be able to go on for the rest of the day. These school turns became very frequent. This is now about twelve years ago. By this time I had found that starvation would relieve me, and that fatty or sweet things would precipitate an attack. Previous to this, I was very fond of sweet things, but somehow I seemed to lose my taste for sweetness in food. About ten years ago I lost a favourite brother by drowning and developed rheumatic fever, and was off duty for five months. Prior to this I had had a great deal of worry and overwork. During this period of rheumatic fever, dizziness was less severe and less frequent. I was superannuated on account of my complaint in 1928 and things went along fairly well for that year and the next. I had, however, always to be on my guard as to diet, since very little upset me. Through 1930 I was very ill and I was just recovering at the time of the Hawkes's Bay earthquake of 1931. After that I spent six weeks in camp, and the open carefree life seemed to help me for a time. I relapsed again, and by the end of the year the dizziness and vomiting were getting extreme. The years 1932 and 1933 have been the most consistently ill of all. These dizzy attacks would often wake me during the night and would occur several times during the day. My vision used to become blurred and distorted and I was in a cold profuse perspiration during and after—often, too, prostrate. No special work precipitated an attack, but worry or anxiety made me very prone to them. Talking to two or three people, being in a crowd, concentration, or the sight of revolving motion, would all bring on attacks. For weeks I never felt hungry, but sometimes after a bout of dizziness or when I could not go to sleep, I could have enjoyed a meal, but desisted for fear of bringing on another attack. When vomiting accompanied my attacks, I slept very heavily and was often hungry. My sleep was very profound. After an attack I used to yawn and yawn. The attacks of dizziness certainly affected my memory and intelligence. I could not think as I wished—the effort was too much for me. Exercise did not bring on attacks. During the past year the symptoms have changed. The attacks are now shorter and more severe and have culminated in my being thrown to the ground on several occasions. The first time was a year ago at Christmas, when, about 3 o'clock in the afternoon, I fell flat on my back. I was not giddy and I did not vomit. The next occasion was three weeks later when I was playing the piano. Before I knew what had happened, I had fallen to the floor. On the third occasion I was shopping and I would have fallen if I had not caught hold of an iron standard. The fourth occasion was immediately before my admission to hospital. I did not feel at all well on rising, but after a cup of tea at about 8.30 a.m. I was chatting to some people on the verandah, when all at once I was seized with that awful sensation. I knew what was impending, as this was my fourth 'throw over'. I grabbed the verandah post, hoping to avert a fall, but my arms just had to relax and down I went. I sat up at once and after a short time I recovered a little, and walked into the house without assistance. In the ordinary attacks of dizziness, I had to have assistance in order to move about at all. I then went to bed and did not feel nearly so ill as generally after even a dizzy attack. In fact, I felt pretty well all day."

On Examination.—The patient was examined about 10 a.m. on Dec. 8, 1933, soon after her last attack. There was slight nystagmus on looking to the right, the abdominal reflexes were not elicited and the left knee- and left ankle-jerks were much brisker than on the right side. The plantar reflexes were flexor. She was admitted to hospital for investigation and when seen a few hours later these abnormal neurological findings were absent.

Her complexion was sallow. Weight, 7 st. 9¾ lb. Height, 5 ft. 4 in. X-ray of the chest showed "considerable elevation of the diaphragm with increase in left subphrenic opacity. There is very definite mottling of both hilar regions and the right cardiophrenic angle. Heart shadow tilted." X-ray shadows of the gall-bladder showed normal function. X-ray of the skull showed a normal pituitary fossa. A twenty-four-hour specimen of urine (32 oz.) showed 100 units of diastase and was otherwise normal. Blood-count: reds 5,000,000 per c.mm., leucocytes 8,600 per c.mm., Hb 96 per cent, colour index, 0·96. Differential count: polymorphs 57·5 per cent, lymphocytes 30·5 per cent, eosinophils 4·5 per cent, transitionals 5 per cent, basophils 2·5 per cent. Reds appear normal. Van den Bergh: direct reaction negative, indirect very weak positive. Fæces were negative for occult blood; films showed no obvious neutral fat globules and no fatty acid crystals; there was a small amount of soap;

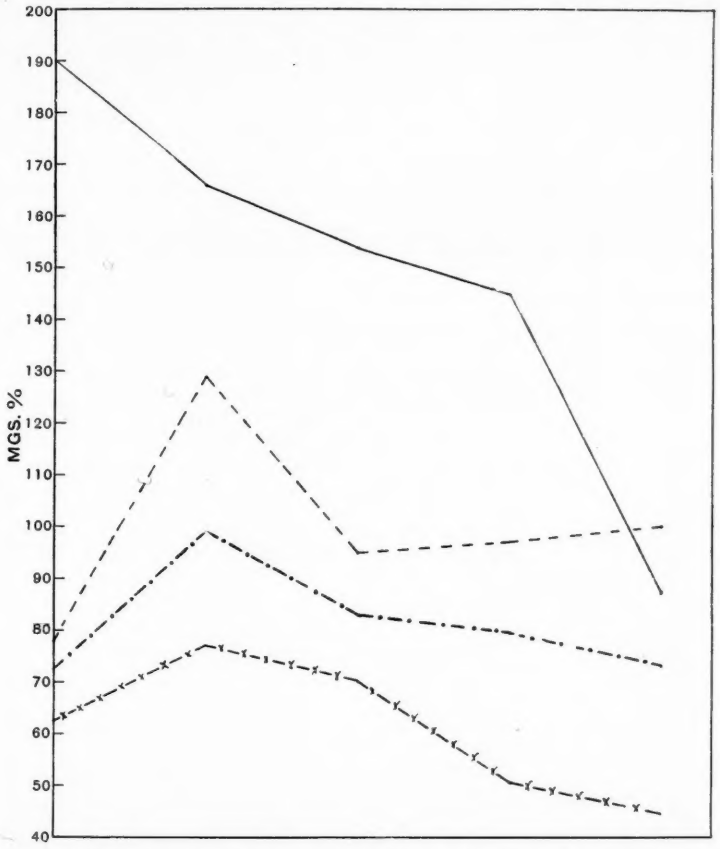


FIG. 39.—Blood-sugar curves with increasing doses of glucose, before operation. –·–·–·–·– Average of three curves after ingestion of 50 grm. of glucose. ———— After ingestion of 100 grm. – – – – – – – – After ingestion of 150 grm. –x–x–x–x–x– After ingestion of 200 grm.

no muscle fibres found. Test-meal showed a normal curve. Blood-pressure: systolic 130 mm. Hg, diastolic 80 mm. Hg. Wassermann and Kahn reactions in blood and cerebrospinal fluid were negative. Neurological and other examinations were normal. There was slight deafness in the right ear, but the tympanic membrane on either side was normal. The thyroid gland was not palpable. The optic discs were normal.

Blood-Sugar Estimations.—A number of blood-sugar estimations were carried out on venous blood by the colorimetric method of Folin and Wu. After the administration of 50 grm. of glucose the curve was always of a hypoglycæmic type, and the average of three such curves before operation is shown in *Fig.* 39. It was decided to carry out tolerance tests with increasing doses of glucose in order to see if any marked difference in the curves resulted. With 100 grm. of glucose the surprising curve shown in *Fig.* 39 was obtained. This curve is referred

to in the discussion. There was a marked difference between the curves obtained after 150 grm. and after 200 grm. of glucose was given (*Fig.* 39). A more detailed curve after the administration of 200 grm. of glucose is shown in *Fig.* 40. The blood-sugar for a fasting day is illustrated in *Fig.* 41. This shows a gradual rise, with a marked rise in the early afternoon. *Fig.* 42

FIG. 40.—Blood-sugar curve after ingestion of 200 grm. of glucose, before operation. The patient had a meal at midday and later complained of a numbed feeling in the hands. The glucose was given at 7.15 a.m.

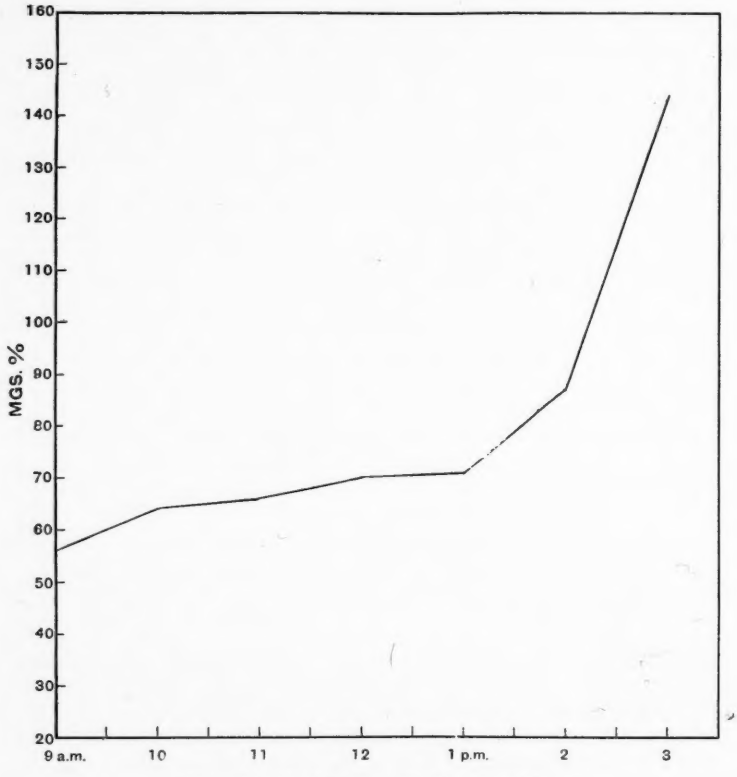


FIG. 41.—Fasting day. Before operation.

shows the curve obtained after 50 grm. of glucose was given with 50 units of insulin intramuscularly. Two and a half hours after the test commenced the blood-sugar was 50 mgrm. per cent, and the patient complained of feeling strange. Three and a half hours after the commencement the capillary blood-sugar was 70 mgrm. per cent, showing that considerable

peripheral storage was therefore taking place at hypoglycæmic levels of blood-sugar, which at the same time was 41 mgrm. per cent. The curve resulting after the administration of 50 grm. of glucose with 1 c.c. pituitary extract intramuscularly is illustrated in *Fig.* 43. The rise in blood-sugar following a subcutaneous injection of 1 c.c. of 1–1000 adrenalin is illustrated in *Fig.* 44. The curve obtained after the administration of 50 grm. of glucose with 2 oz. of brandy is shown in *Fig.* 45. This curve does not differ materially from those obtained after the administration of 50 grm. of glucose alone.

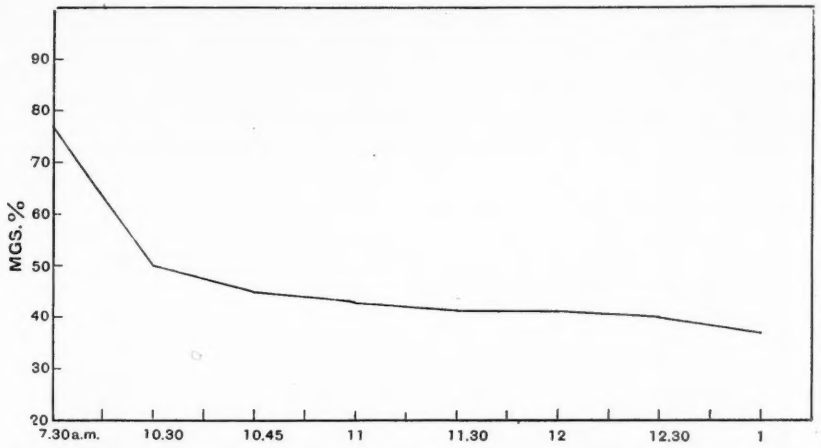


FIG. 42.—Blood-sugar curve before operation, after 50 grm. of glucose by mouth and 50 units of insulin intramuscularly at 8 a.m. At 10.30 a.m. the patient complained of feeling strange. Capillary blood-sugar at 11.30 a.m. was 70 mgrm. per cent.

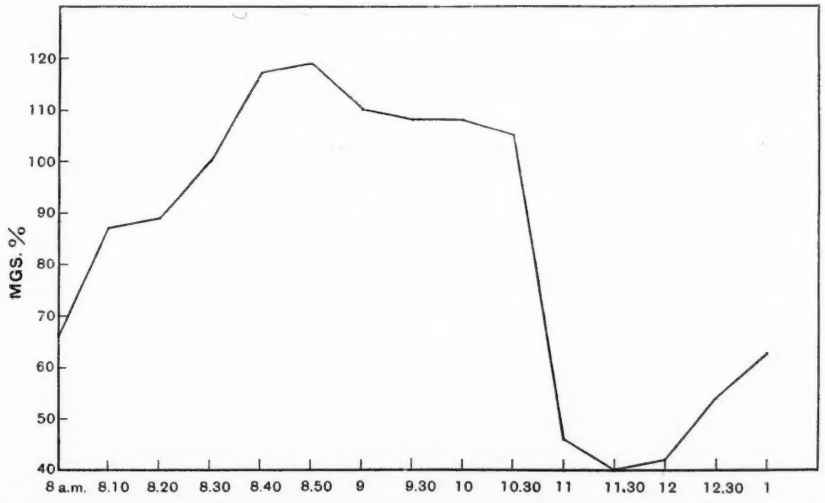


FIG. 43.—Blood-sugar curve before operation after 50 grm. of glucose by mouth and 1 c.c. of pituitrin intramuscularly.

After a consideration of the various blood-sugar tests the case was thought to be one of hyperinsulinism, and operation was decided upon.

OPERATION (Jan. 24, 1934).—I.M.H. gr. $\frac{1}{6}$ and hyoscine hydrobromide gr. $\frac{1}{150}$ were given at 7 a.m., followed by 5 drachms of paraldehyde with 70 drachms of saline per rectum. In the operating-theatre 250 c.c. of ether was administered. A left paramedian incision was made with a lateral incision into the flank. The pancreas and other abdominal organs were examined and found to be normal. A little more than 28 grm. of pancreas, including the

tail and part of the body, were removed, going through the gastro-hepatic omentum. The operation was technically difficult owing to the fact that the pancreatic veins were exceedingly fragile, tearing out of the splenic vein and needing several lateral ligatures on that vessel. One of the splenic veins during the removal of the tail caused troublesome bleeding. It was

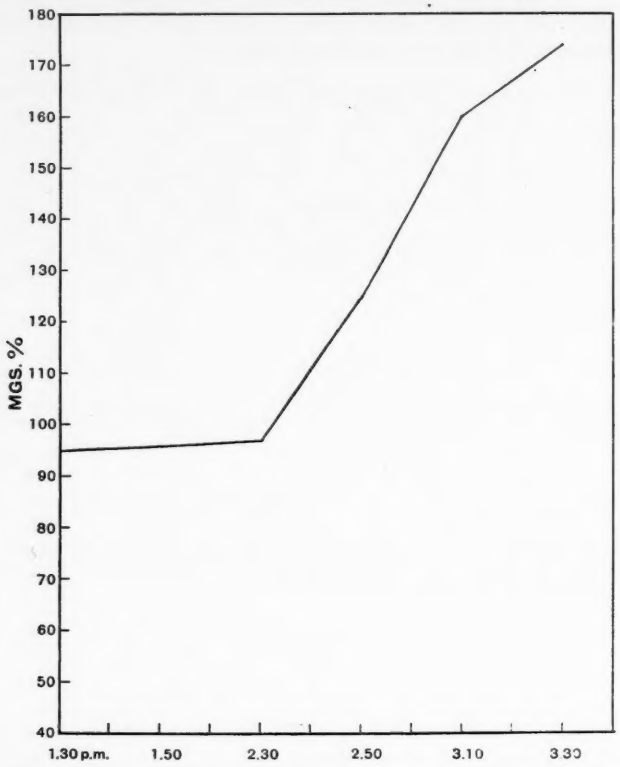


FIG. 44.—Blood-sugar curve before operation after 50 grm. of glucose by mouth and 1 c.c. of 1–1000 adrenalin solution injected subcutaneously at 1.50 p.m. At 3.25 p.m. the capillary blood-sugar was 181 mgrm. per cent.

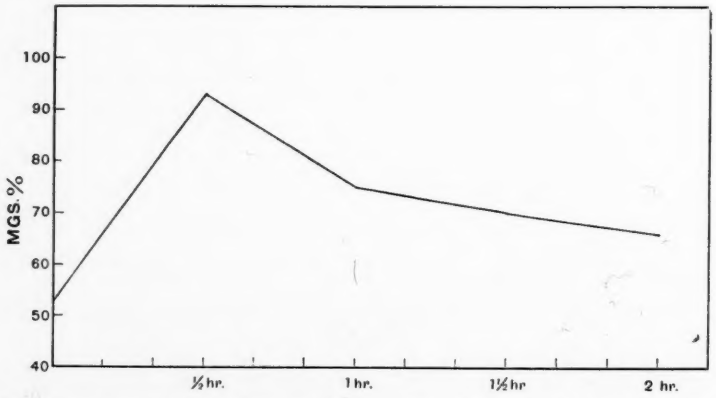


FIG. 45.—Blood-sugar curve before operation after ingestion of 50 grm. of glucose with 2 oz. of brandy.

intended to remove somewhat more of the pancreas, but a large vein passed through the body upwards and towards the left to join the splenic vein. Rubber-covered clamps were applied as close as possible and parallel to this vein, and that portion of the pancreas to the left was removed. The clamps were left in position and removed on the third day.

Following the operation the patient was shocked. At 11.30 a.m. one pint of blood with two pints of saline and gum acacia were given intravenously. At 4 p.m. two pints of 5 per cent glucose with 60 units of insulin were given. At 8 p.m., 6 oz. of urine were passed which contained sugar. On the following morning the patient's condition was satisfactory. The urine contained a large amount of sugar but no acetone bodies. In the evening another blood transfusion of one pint was given. The highest temperature was on the second day following operation, when it reached 102°, and by the fifth day it was normal. There was some serous and later some purulent discharge from the track along which the clamp and forceps had lain, but the wound healed satisfactorily. On Feb. 22 the patient complained of some frequency of micturition. A catheter specimen of urine showed microscopical pus, a number of epithelial cells, and Gram-positive bacilli. This condition persisted for some weeks and bladder irrigations were necessary. The pathological report on the pancreas was: "The structure is that of a normal pancreas. The amount of insulin tissue judged by comparison with a normal pancreas is not more than normal. There is no inflammatory change in the pancreas."

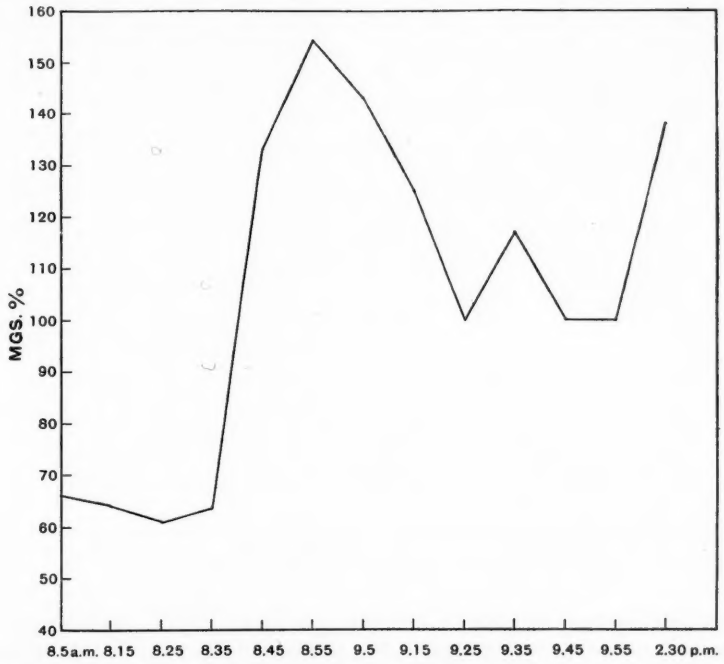


FIG. 46.—Blood-sugar curve during operation. Paraldehyde administered at 8.15 a.m. Ether commenced at 8.45.

Blood-sugar estimations were done at intervals of ten minutes before, during, and after operation (*Fig.* 46). These figures show that the blood-sugar, as is well known, rises during the course of a surgical operation, particularly when ether or chloroform is used.

AFTER-PROGRESS.—While the patient was in hospital she had many attacks of vertigo. Glucose-tolerance tests were carried out during convalescence. Four weeks after operation a diabetic type of curve was obtained after the administration of 50 grm. of glucose (*Fig.* 47). Three months after operation, the curve, after a similar test, had returned almost to what it was before operation (*Fig.* 47). The patient's weight fell from 7 st. 10 lb. to 7 st. 5 lb. a week before operation. When she was next weighed (March 2) she was 6 st. 9 lb.; on March 17, 7 st. 3 lb. On her discharge from hospital on April 14 her weight was 7 st. 8 lb. Writing recently the patient stated:—

"On June 14 my weight was 9 st. 1 lb. and it has increased to 9 st. 6 lb. at the time of writing, which is my greatest weight for fourteen years. After leaving hospital I had a few touches of dizziness, but these attacks were different from those of the

pre-operative period. They were more transitory in nature—very much less severe—in short, not to be compared with the previous ones. I could, even if slightly dizzy, move about on my own, which was more than was possible previously. I was conscious of a gradual improvement in every way. I can enjoy food and take various articles of diet that I had not cared to touch before, and I have noticed that I want my tea sweeter. I feel every bit as good as I did twenty-five years ago when I enjoyed perfect health. I cannot realize my freedom from that awful affliction."

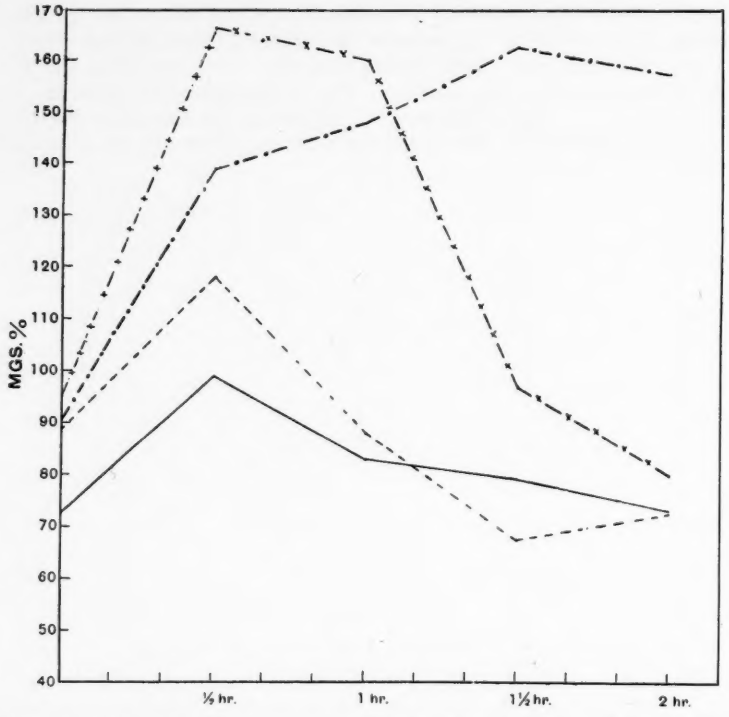


FIG. 47.—Comparison of blood-sugar curves after ingestion of 50 grm. of glucose before and after operation. ———— Before operation. –·–·–·–·– One month after operation. – – – – – – – – Three months after operation. –x–x–x–x– Eight months after operation.

Fig. 47 illustrates in a striking manner the readjustment of carbohydrate metabolism. The hypoglycæmic curve before the operation is shown. Then within four weeks of operation a diabetic type of curve. This was followed three months after operation by a return of the curve almost to its original hypoglycæmic level. Again, eight months after operation the curve is practically normal.

DISCUSSION

Cases of hypoglycæmia may be divided into: (1) Those due to functional hyperinsulinism, whether due to increased number, size, or activity of the islands of Langerhans. (2) Those due to the presence of an adenoma or carcinoma of the pancreas. (3) A medley of cases which come under the heading of 'dysinsulinism.' These are dependent on pituitary, adrenal, hepatic, or other factors.

From a perusal of the literature it would appear that the surgical treatment of spontaneous hypoglycæmia, apart from those cases in which an adenoma has been removed, is disappointing. The possibility must be considered that those cases of hyperinsulinism that have not responded to surgical treatment may have

had a small adenoma buried in the head of the pancreas, where it would be difficult or impossible to locate on account of its size.

Best[3] publishes the following table :—

Cases with no detectable pancreatic lesion (Finney, Holman, Allen 2, Mayo 2)	6
Cases without tumour in which partial pancreatectomy was performed	6
Results of partial pancreatectomy :—	
Reports of improvement unconvincing	1
No improvement reported	5

With such disappointing results, it is not surprising that John[4] should state : " The operative procedure, with the exception of cases in which there is an adenoma of the pancreas, does not seem a logical solution of the problem of hypoglycæmia."

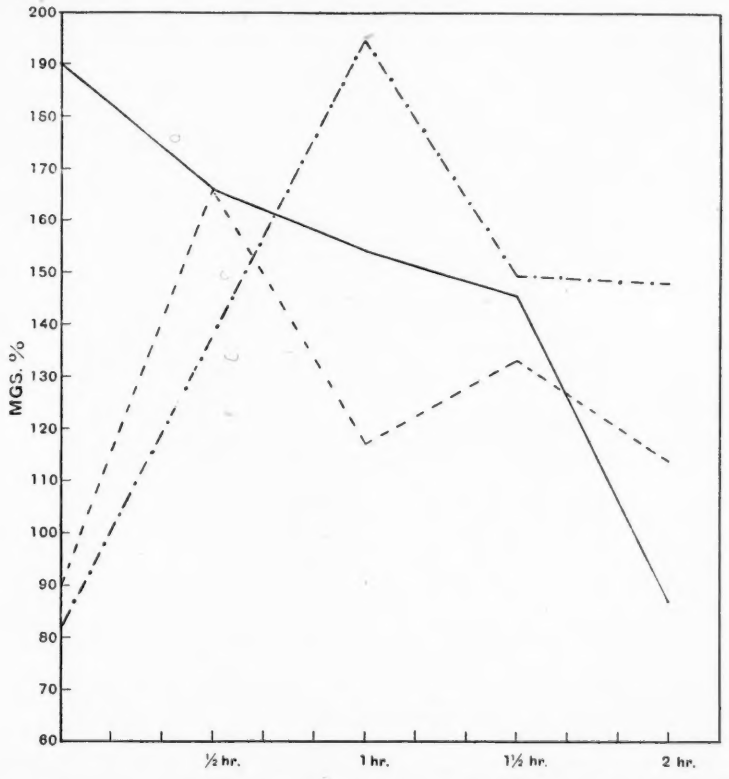


FIG. 48.—Comparison of blood-sugar curves after ingestion of 100 grm. of glucose before and after operation. ———— Before operation. -·-·-·-·- Five weeks after operation. – – – – – – – – Eight months after operation.

He regards these cases as potentially diabetics, and on this basis treats them by insulin after meals, hoping to avoid hyperglycæmia and to prevent the high blood-sugar stimulating an excess of insulin. By supplying exogenous insulin he attempts to put the pancreas at rest.

Nielsen and Lewis,[5] in a discussion on glucose-tolerance tests in patients with vagotonia, state that these patients experience with peculiar regularity a hypoglycæmic reaction during the course of a glucose-tolerance test. In 21 cases

there were 3 in which the blood-sugar fell immediately after ingestion of 100 grm. of glucose. They concluded that the pancreas was very active, that it was stimulated easily, and acted quickly. In one of their cases the highest point in the course of the test was found in the starvation specimen. In the present case this phenomenon is well illustrated in *Figs.* 39 and 48.

Brougher,[6] in a study of glucose-tolerance tests in 14 patients whom he regarded as hypoglycæmic, noted the frequency with which hypoglycæmic symptoms occurred during the course of the test. In the present case the administration of glucose with insulin was followed by a period in which the patient complained of feeling strange and there was a definite and gradual fall in the blood-sugar (*see Fig.* 42). It would appear that, though the administration of insulin in these

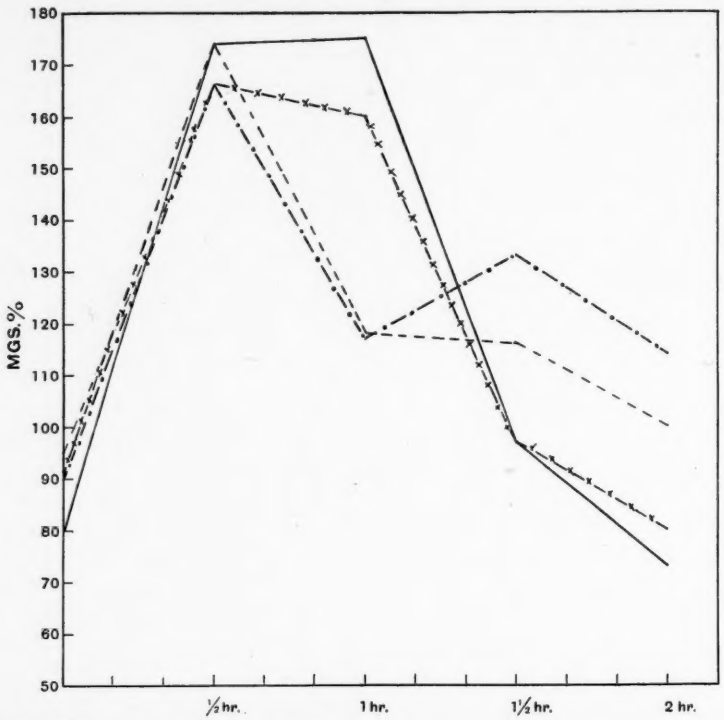


FIG. 49.—Blood-sugar curves with increasing doses of glucose eight months after operation. -x-x-x- After ingestion of 50 grm. of glucose. -•-•-•-•- After ingestion of 100 grm. - - - - After ingestion of 150 grm. ———— After ingestion of 200 grm.

cases may possibly be indicated theoretically, a study of the blood-sugar curve shows that hypoglycæmia is not avoided. It must be noted, however, that Nielsen and Lewis in their conclusions in the paper referred to state: "The hypoglycæmic reaction is not necessarily coincident with hypoglycæmia. There is still some unexplained factor in the production of these reactions. The degree of the reaction bears no direct relation to the depth of the glucose-tolerance curve." It may be possible to associate abnormal curves during a tolerance test with the subjective symptoms of the patient, even though the degree of hypoglycæmia is not necessarily related to the symptoms. The striking blood-sugar curve shown in *Figs.* 39 and 48 after the ingestion of 100 grm. of glucose showed a fasting blood-sugar of 190 mgrm. per cent. This is a very anomalous curve. At 2 a.m. on the day of

the test the patient had a severe attack of vertigo. It was so severe that she said she would certainly have fallen had she been standing. It is possible that the rise in blood-sugar recorded was a compensatory phenomenon, as the test was begun about five hours later at 7 a.m.

Since removal of an adenoma is accompanied by such excellent results, it seems logical that resection of an amount of pancreas equivalent to the hyperinsulinism is the ideal treatment. From the recent blood-sugar curves of the present case (*Fig.* 49), it seems clear that the patient might have been better with a greater removal of pancreatic tissue. Should hypoglycæmia reappear, it would be almost surgically impossible to remove more pancreatic tissue on account of the superior and inferior mesenteric veins passing through the body of the pancreas. Exactly how much pancreas should be removed is a question that will depend on the severity of the symptoms and on the size of the pancreas. In the past resections have certainly been much too small to allow of any permanent improvement. *Table I* shows the amount of pancreas that has been removed in the recorded cases.

RESECTION OF PANCREAS IN HYPERINSULINISM

OBSERVER	AMOUNT OF PANCREAS REMOVED	RESULT
Finney and Finney[7]	22·5 grm.	Slight improvement
Judd[9]	14 grm.	Improvement lasted one year. Later condition worse than before operation
Judd[9]	8 grm.	No improvement
Judd[9]	5 grm.*	No improvement
Holman and Judd[9]	Weight not stated (2 operations)	Slight improvement
Ziskind[10]	7·2 grm.	No improvement
Wormack[11]	"About half" (2 cases)	Improvement
Graham and Hartmann[8] ..	80 to 90 per cent	Improvement

* At subsequent operation a piece of pancreas was clamped and allowed to slough away.

Probably half of the pancreas should be removed to obtain satisfactory results. In the classical case recorded by Finney and Finney[7] it is stated that two-thirds of the pancreas was removed, this weighing 22·5 grm. In a footnote the weight of a normal pancreas in a woman is given as 60 grm. It would appear more accurate to describe this resection as one-third of the pancreas unless the organ in their patient was smaller than normal. It would seem that the figures given for dogs—namely, that 80 to 90 per cent of the pancreas has to be removed to cause hyperglycæmia or glycosuria—are much too high for man. There does seem a distinct liability that a patient might be converted into a permanent diabetic by removal of considerably more than half of the pancreas. The diabetic tendency of the present patient lasted only for a short time (*see Fig.* 47). Then there seemed to be an increased activity of the remaining insulin tissues and her condition seemed to have returned almost to her former state (*see Fig.* 47). Since then there has been a change of the blood-sugar curve almost to normal.

In the striking case recorded by Graham and Hartmann,[8] 80 to 90 per cent of pancreatic tissue was removed from a child of 12 months. The blood-sugar, although at first raised to an abnormally high level as a result of removal of so much pancreatic tissue, later became practically normal, and nine months after operation the fasting blood-sugar was 83 mgrm. per 100 c.c. In discussing this case the authors state: "It becomes evident from this brief review of the reported cases that in general the resection of an approximately normal pancreas up to the amount of two-thirds of it (quoting Finney and Finney) is not likely to result in permanent improvement of the chronic hypoglycæmic, except rarely." In view of the doubt as to whether two-thirds of the pancreas was removed in the Finneys' case and of the great improvement in the present case, it would seem that this statement is not in accordance with the facts. On the analogy of thyroid surgery they state: "In line with such reasoning, one might suppose that the failure to obtain permanent and satisfactory results in the majority of cases in which a true tumour has not been found might have been due to the removal of too little pancreatic tissue." In the same article Wormack, of St. Louis, is quoted as having removed half the pancreas in two cases with subsequent alleviation of hypoglycæmic symptoms. Judd,[9] in another paper, states: "The results thus far have not been encouraging, probably because not enough gland has been removed to influence adequate production of insulin. Medical treatment has proved unsatisfactory in cases in which there was a strong tendency to hypoglycæmia." It would seem reasonable to assume that in cases of functional hyperinsulinism the success of surgical treatment of hyperthyroidism will be repeated if sufficient amounts of pancreas are removed, and it is along surgical lines that cure or alleviation of symptoms is to be expected.

If it were possible to distinguish cases of functional hyperinsulinism from those of adenoma of the pancreas, it might be possible before operation to state how much pancreas should be removed. Wilder,[12] in a discussion on hyperinsulinism, states: "The clinical differentiation between cases with and those without tumour has been for us impossible. The severity of the symptoms has been great in both groups of cases. The dextrose-tolerance test has not been helpful."

In reviewing the records concerning cases of spontaneous hypoglycæmia there is no mention of the study of increasing amounts of carbohydrate on the blood-sugar curves. It would seem probable that cases of marked functional hyperinsulinism should react to increasing amounts of carbohydrates by a progressive lowering of the blood-sugar, and that starvation, on the other hand, should allow the blood-sugar to rise. If these postulates should prove true in other cases, then functional hyperinsulinism, whether due to increased number, size, or activity of the islands of Langerhans, should easily be separated from other causes of hypoglycæmia. From a study of the blood-sugar curves in those cases of spontaneous hypoglycæmia due to the presence of an adenoma or carcinoma of the pancreas it is suggested that these tumours are not under nervous or hormonic control and that they are continually secreting insulin. It has also been suggested that there is a secretion from the tumour itself which stimulates insulin secretion.

On examining the numerous blood-sugar curves that were carried out in the present case before operation it was evident that with large doses of glucose the blood-sugar tended to fall, while eight months after operation different doses of

glucose gave almost the same curve (*see Fig.* 49). Doses larger than 200 grm. were not used in any of the tests. On comparing the curves after the administration of 50 and 200 grm. of glucose respectively (*see Figs.* 39 and 50), it will be seen that the curve after the 200-grm. test is continually lower than after the 50-grm. test. The stomach contents were not aspirated and tested for glucose at the end of the tests and it may be argued that there was delayed absorption of glucose owing to the stomach's emptying slowly. As the 200-grm. test was carried out over a period of practically four hours it seems that this argument would not apply. If the pancreas is abnormally sensitive and easily stimulated in functional hyperinsulinism, it seems reasonable to suppose that the greater the amount of glucose

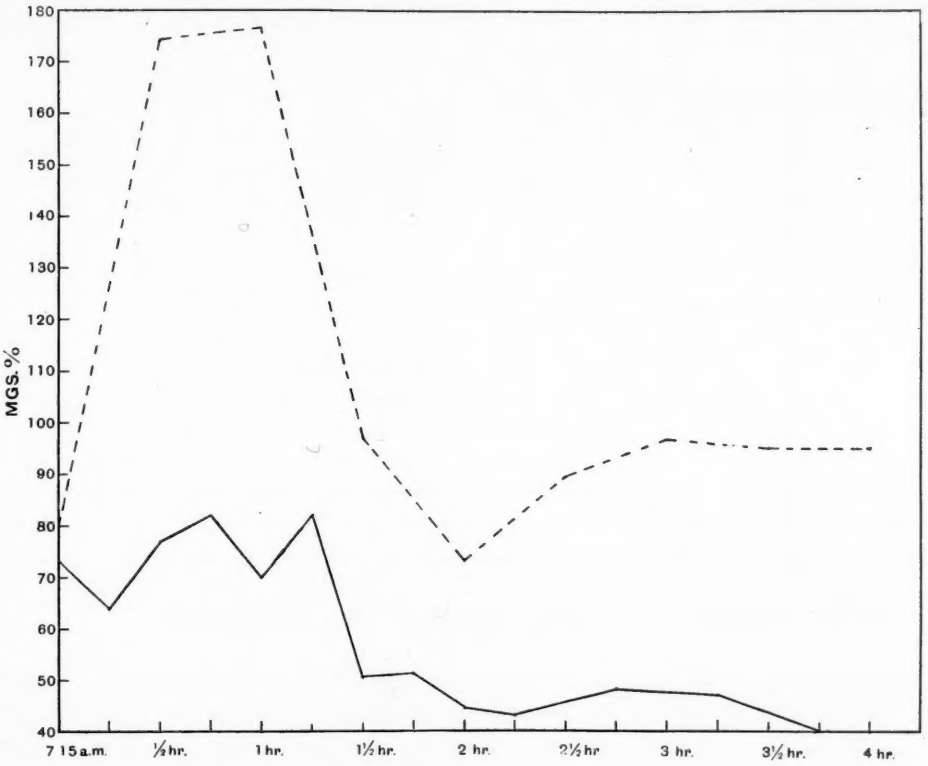


FIG. 50.—Comparison of blood-sugar curves after ingestion of 200 grm. of glucose before and after operation. ——— Before operation. - - - - - After operation.

absorbed into the blood-stream, the greater will be the stimulus to the production of insulin. Hence the decreasing values in the blood-sugar curves with increasing doses of glucose. If it should be proved definitely that the excessive insulin production in a case of adenoma is not dependent on hormonic, nervous, or other control, this test should prove of great value in the differentiation of tumours of the pancreas from functional hyperinsulinism.

It is well known that during starvation the level of the blood-sugar falls very little, and lowering it beyond a certain level cannot be effected by complete deprivation of food, however prolonged. In this case starvation actually resulted in a rise in blood-sugar (*see Fig.* 41). It is difficult to understand why this should occur.

Possibly there was a lack of stimulus to the pancreas during the period of starvation and consequently insulin production was diminished, allowing the blood-sugar to rise. It would have been expected that when the blood-sugar had reached a certain value, more insulin would have been produced, causing a hypoglycæmic reaction. It is suggested that this rise in blood-sugar during starvation may be confined to cases of functional hyperinsulinism and may prove a ready means of distinguishing this condition from a tumour of the pancreas. It is hoped that, by drawing attention to this phenomenon and to the probability that large doses

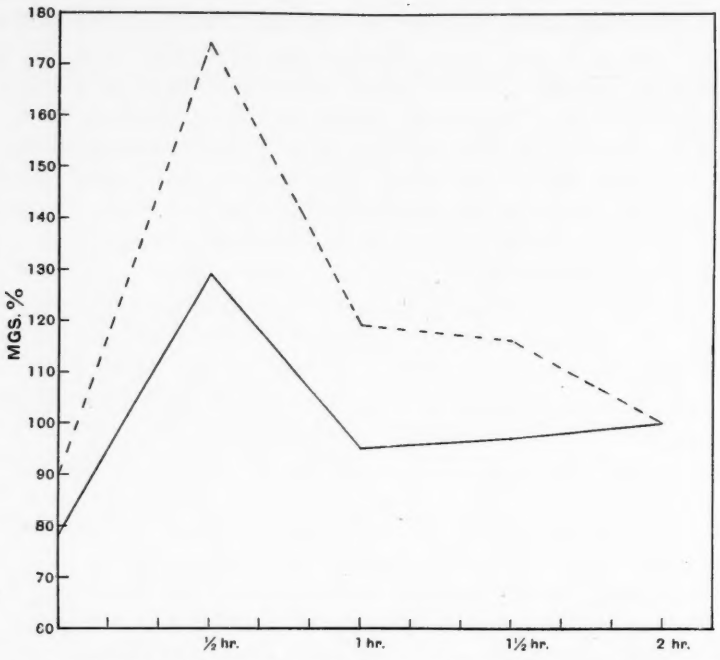


FIG. 51.—Comparison of blood-sugar curves after ingestion of 150 grm. of glucose before and after operation. ———— Before operation. - - - - - After operation.

of glucose in cases of functional hyperinsulinism lower the blood-sugar, these tests will be carried out in future cases of spontaneous hypoglycæmia in which surgical intervention is contemplated. Only by this means can the value of these tests be proved.

SUMMARY AND CONCLUSIONS

1. A case of hyperinsulinism is described.
2. Partial pancreatectomy was performed, 28 grm. of pancreas being removed.
3. Glucose-tolerance tests performed before and after operation are discussed.
4. The following hypotheses are put forward: (*a*) Adequate resection, probably more than half of the pancreas, in a moderately severe case of functional hyperinsulinism is necessary to alleviate symptoms. (*b*) In the diagnosis of functional hyperinsulinism increasing doses of glucose are necessary in preparing blood-sugar curves, and the curves are lower with the large doses. (*c*) In functional hyperinsulinism starvation causes a rise in blood-sugar.

5. It is suggested that these two tests may be of value in distinguishing functional hyperinsulinism from an adenoma or carcinoma of the pancreas.

I wish to thank Messrs. S. W. Saunders and G. W. McKinley for performing the numerous blood-sugar estimations in this case.

REFERENCES

[1] WAUCHOPE, G. M., *Quart. Jour. Med.*, 1933, Jan., 117.
[2] WILDER, R. M., *Internat. Clinics*, 1933, June, 1.
[3] BEST, C. H., *Lancet*, 1934, i, 1157.
[4] JOHN, H. J., *Med. Clin. N. Amer.*, 1934, xvii, 979.
[5] NIELSEN, J. M., and LEWIS, W. B., *Arch. Pathol. and Lab. Med.*, 1927, iii, 212.
[6] BROUGHER, J. C., *Northwest Med.*, 1934, xxxiii, 125.
[7] FINNEY, J. M. T., and FINNEY, J. M. T., Jr., *Ann. of Surg.*, 1928, lxxxviii, 584.
[8] GRAHAM, E. A., and HARTMANN, A. F., *Surg. Gynecol. and Obst.*, 1934, Sept.
[9] JUDD, E. S., *Jour. Amer. Med. Assoc.*, 1933, ci, 99.
[10] ZISKIND, E., *Arch. of Internal Med.*, 1933, lii, 76.
[11] WORMACK, quoted by GRAHAM and HARTMANN.
[12] WILDER, R. M., *Jour. Amer. Med. Assoc.*, 1933, ci, 1964.

CONGENITAL DERMOID CYSTS AND SINUSES OF THE LIMBS

By M. J. BENNETT-JONES
SURGICAL REGISTRAR, LIVERPOOL ROYAL INFIRMARY

CONGENITAL dermoid cysts and sinuses associated with the limbs appear to be very rare and to have escaped description in the English surgical literature. Dieterich, however, records a dermoid cyst of the shoulder, and Phélip has described a congenital dermoid cyst occurring on the index finger of an infant aged 13 months. Epiphanov has also described a cystic dermoid femoral hernia. Apart from these cases, Paterson, Cisneros, and others have described dermoid cysts occurring in

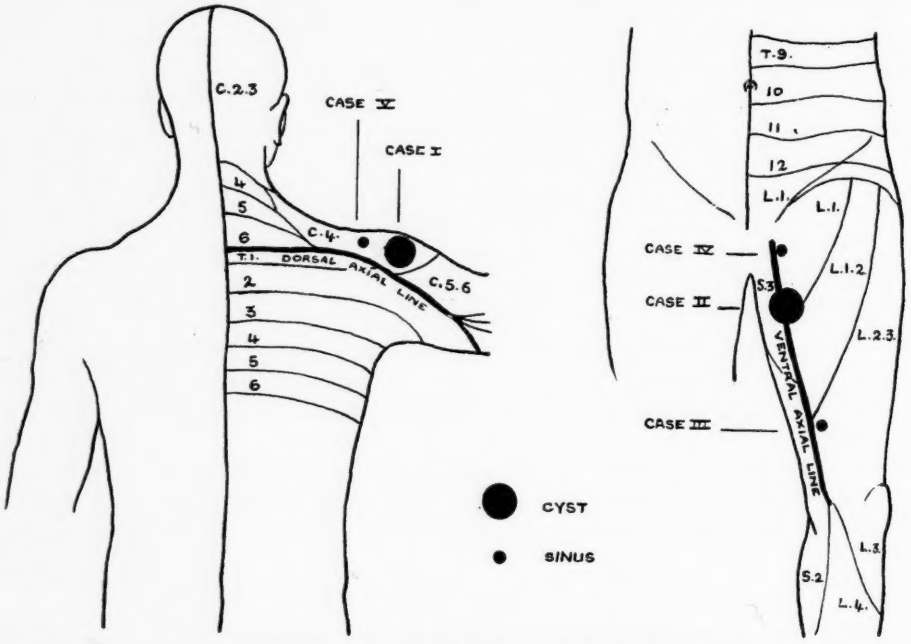


FIG. 52.—Diagram showing dorsal and ventral axial lines and the sites of the congenital dermoid cysts and sinuses recorded.

the inguinal canal, and Bland-Sutton has recorded the removal of a very large dermoid cyst of the right labium majus; these latter cases, however, did not occur on the limbs, although they probably had the same etiology.

Etiology.—The limbs arise as buds from the ventro-lateral aspect of the trunk and they are composed of a number of body segments. Owing to the fact that the more peripheral part of the limbs is derived from the middle segments of the limb bud, there is formed a dorsal and ventral axial line in the proximal portions of the limbs, between the upper and lower segmental portions. These

axial lines appear to be the most common site for dermoid cysts and sinuses associated with the limbs (*Fig.* 52).

Clinical Features.—In the appended short series of cases a dermoid cyst and dermoid sinus were seen near the tip of the shoulder. This position marks the boundary between the areas of skin supplied by the cervical and brachial plexuses; this position is also very near, if not coincident with, the dorsal axial line of the upper limb.

In the lower limb three cases were seen. A dermoid sinus was observed between the posterior end of the labium majus and the thigh. A dermoid cyst was removed from the inner side of the upper third of the thigh, and a dermoid sinus was seen on the inner aspect of the lower third of the thigh. It is interesting to note that these three cases occurred on the ventral axial line of the lower limb.

Two cases were associated with other congenital deformities. The sinus between the thigh and the labium majus was associated with a recto-vaginal fistula and spina bifida occulta; and the sinus in the lower third of the thigh was associated with an accessory hallux.

Conclusion.—Although both the dermoid cysts were diagnosed as lipomata, these cases have no great surgical importance. This series, supported by Phélip's case, does, however, raise the possibility that some, at least, of the so-called traumatic epithelial cysts of the hand may be congenital in origin. These cases, however, have an embryological significance and they help to confirm Sherrington's work on the segmental nerve-supply of the limbs which was worked out experimentally on apes.

CASE REPORTS

Case 1.—Male, aged 23. Admitted into the Liverpool Royal Infirmary.

HISTORY.—A swelling on the right shoulder was noticed soon after birth. It enlarged very slowly, but lately became tender and the overlying skin became red, so that the patient desired removal of the swelling.

ON EXAMINATION.—Very soft, fluctuant, non-translucent swelling situated in the subcutaneous tissue superficial to the acromion process near its tip. The swelling was about 1½ in. in diameter and was not lobulated. The adherent overlying skin was tense and red.

OPERATION (Mr. Nuttall, Dec. 9, 1933).—The tumour was found to be a dermoid cyst and was, therefore, easily excised.

PATHOLOGICAL REPORT (Dr. T. B. Davie).—The cyst is lined by typical squamous epithelium of a dermoid.

Case 2.—Female, aged 32. Admitted into the Liverpool Royal Infirmary.

HISTORY.—A lump appeared on the inner side of the left thigh at least ten years ago. It enlarged very slowly, but at times it became painful and slightly tender. After the operation the patient was questioned about any possible injury or puncture of the thigh, but neither could be remembered. Lately another lump appeared in the right groin which caused the patient to seek advice.

ON EXAMINATION.—Spherical, non-translucent, fluctuant swelling about 1½ in. in diameter situated on the inner aspect of the upper third of the left thigh. No attachment to the overlying skin or the underlying adductor magnus muscle. No impulse on coughing. The lump in the right groin was a typical femoral hernia.

OPERATION (Mr. Nuttall, Oct. 12, 1933).—Repair of right femoral hernia by Lotheissen's method. Excision of a cyst of the left thigh, which was found to be a typical dermoid cyst.

PATHOLOGICAL REPORT (Professor Dible).—Squamous epithelial cyst.

Case 3.—Male, aged 2. Admitted into the Hospital for Sick Children, Great Ormond Street.

HISTORY.—The child's mother brought him to hospital because an accessory toe prevented

his obtaining shoes which fitted. The child also had a sinus on the inner side of the left thigh which had been present since birth. Occasionally a swelling appeared deep to the sinus, but it soon disappeared by discharging through the sinus.

ON EXAMINATION.—Small epithelial sinus on the inner aspect of the lower third of the left thigh, superficial to the internal intermuscular septum. No swelling deep to the sinus at present, but a swelling was seen in the Out-patient Department. An accessory left hallux was present.

SUBSEQUENT HISTORY.—

Oct. 29, 1932.—Mr. Tyrrell-Gray amputated the 2nd toe including its metatarsal after consultation with Mr. Fairbank, but no operation was performed on the sinus.

Jan. 5, 1935.—The mother states that the sinus is giving no trouble at present, although it occasionally discharges.

Case 4.—Female, aged 8 months. Under the care of Mr. W. A. Thompson at the Royal Liverpool Children's Hospital.

HISTORY.—The child was brought to hospital on account of a recto-vaginal fistula. The mother also noticed a sinus near the right labium majus which occasionally discharged.

ON EXAMINATION.—A recto-vaginal fistula was present associated with an imperforate anus and spina bifida occulta. Epithelial sinus situated between the posterior end of the right labium majus and the right thigh. No discharge at present.

Case 5.—Female, aged about 50. A patient of Mr. Grant Massie at Guy's Hospital.

HISTORY.—For many years she had a sinus near the tip of the right shoulder which discharged intermittently.

ON EXAMINATION.—Sinus near the tip of the right shoulder, with the typical foul smell of decomposing dermoid secretions.

SUBSEQUENT HISTORY.—She became frightened after a demonstration and she did not turn up again, and could not be traced.

This case, therefore, is not confirmed by operation and there was no proof that the sinus was congenital, but at the time it was thought to be a dermoid sinus, and, moreover, it occurred in the same situation as the dermoid cyst on the shoulder (*Case* 1).

I wish to thank the surgeons of the various hospitals for permission to record their cases.

BIBLIOGRAPHY

PATERSON, H. J., *Trans. Pathol. Soc.*, 1903, liv, 147.
PHÉLIP, *Bull. et Mém. Soc. Anat. de Paris*, 1919, lxxxix, 285.
KEITH, SIR A., *Human Embryology and Morphology*, 1921.
BLAND-SUTTON, SIR J., *Tumours, Innocent and Malignant*, 1922.
EPIPHANOV, N., *Vesnik Khir.*, 1927, x, 179.
DIETERICH, H., *Arch. f. klin. Chir.*, 1929, clv, 179.
CISNEROS, R., *Bol. y. Trab. de la Soc. de Cir. de Buenos Aires*, 1930, xiv, 774.

ACROMEGALY

By R. LAWFORD KNAGGS, Newton Abbot

"Acromegaly is a chronic disease of adult life outwardly characterized by the acral changes first emphasized by Marie", and believed to be dependent on a hyperplasia of certain granular cells in the anterior lobe of the pituitary body, which in many instances produces an enlargement or a tumour (Cushing and Davidoff).

A Synopsis of the Pituitary Disorders.—The growth disorders known as acromegaly, giantism, and infantilism constitute a group of affections which are believed to depend largely upon abnormalities of pituitary gland secretion. Besides having a common glandular origin they are further correlated. Giantism tends to merge into acromegaly, and acromegaly, after persisting for a number of years, acquires some of the features of infantilism.

There is no doubt that giantism and acromegaly result from excessive secretion of the anterior lobe, usually as a consequence of hyperplasia of its cells, though in rare instances it may possibly be due to their physiological over-activity; on the other hand, the supervention of some of the signs of infantilism is supposed to mark the waning of the hypersecretion and the access of a state of deficient secretion (hyposecretion) resulting from the inaction or exhaustion of the anterior lobe.

The following scheme of the conditions dependent upon abnormalities of the pituitary secretion has been compiled from Harvey Cushing's *Pituitary Body and its Disorders* (1912), a book so full of clinical and experimental facts that in the future much valuable information will be quarried from it.

Cushing recognized three symptom-groups determined by variations of the pituitary secretion: (1) Hyperpituitarism, in which the anterior lobe secretion is increased (over-activity); (2) Hypopituitarism, in which the anterior lobe secretion fails or is insufficient (under-activity); and (3) Dyspituitarism, in which the symptom-groups are mixed, and it may be difficult to tell whether the hyper- or the hypopituitary state predominates. These are transition cases, and constitute the majority.

1. *Hyperpituitarism.*—From hyperpituitarism result:—
   - *a.* Giantism, when the process occurs before the epiphyses have united with the shafts of the long bones (Type of Launois).
   - *b.* Acromegaly, when it occurs later—in adult life (Type of Marie).
2. *Hypopituitarism.*—
   - *a.* When the disorder originates in childhood there is adiposity with skeletal and sexual infantilism (Type of Fröhlich).
   - *b.* In some cases adiposity is absent—"an adult in a small mould" (Type of Lorain).
   - *c.* When the affection begins in adult life it produces adiposity and sexual infantilism of a reversionary type; i.e., sexual adolescence occurs before the symptoms of hypopituitarism develop (Type of Harvey Cushing).

3. *Dyspituitarism.*—In dyspituitarism the signs of pituitary under-activity constitute the striking feature, but manifestations of a previous hyperpituitarism in the shape of acromegalic changes are present.

4. Cushing included under dyspituitary states two case-groups. His fourth group—in which secondary disturbance of the pituitary is produced by remote, rather than local, intracranial lesions; and

5. His fifth group, in which the signs and symptoms point to involvement of several of the ductless glands—the *pluri- or polyglandular affection.* It is the latter group with which acromegaly is sometimes associated.

INTRODUCTION

The year 1886 is a landmark in the story of acromegaly. Before that date certain peculiar appearances, seen in rare and occasional cases, had attracted attention, but they were not understood, even when Pierre Marie,[1] in a celebrated paper, described the condition and showed that it was identical with that depicted in a number of recorded cases. As a result of his observations Marie concluded that "there exists an affection characterized chiefly by hypertrophy of the feet, hands, and face, which I propose to call 'acromegaly', that is to say, hypertrophy of the extremities"; "not," he added, "that in reality the extremities only are attacked during the duration of the malady, but because their increase in size is an initial phenomenon, and constitutes the most characteristic feature of the affection."

A descriptive record of these early cases is readily accessible in the monographs of Sternberg and Souza-Leite* translated respectively by F. W. Atkinson and P. S. Hutchinson,[2] but a few of the more notable ones are referred to below to give a general impression of the disease as it was understood after the publication of Marie's article.

Case 1.—The first case in England of which there is any note was a certain Richard Dickenson (*Fig.* 53), a shoe-cleaner and vendor of gingerbread, who subsequently became 'Governor of Scarborough Spaw (Spa) and lavatory attendant' He was, in his way, a celebrity, and well known to visitors. He died in 1738 at the age of 68. Five different portraits of him are extant, and three were reproduced in an interesting account by L. P. Mark.[3] They show the characteristic signs of acromegaly and, in addition, deformities which were probably due to rickets.

Case 2.—Henrot gave to this case the name of "general progressive hypertrophy" (1877), and it is of special importance because a pituitary tumour was present. The particulars are as follows: Alphonse D— was 38 years old when he died. From the age of 6 he had general increasing swellings of the submaxillary cervical glands, which never suppurated, and eventually filled the whole front of the neck and overlapped the lower jaw. The blood showed no leucocythæmia. He noticed progressive enlargement of the hands and feet from the age of 15, was in a dragoon regiment at 20, and for the last five years of his life worked in the cellars (Rheims). His face was repulsive, his appetite large, and his thirst abnormal. For the rest, it is sufficient to quote the abstract which prefaces the account:[4] "Cervical adenia; slight

* The earliest known suggestion of acromegaly occurs in a sculptured figure on Rheims Cathedral (thirteenth century). Art frequently makes use of diseased conditions to represent the grotesque, and a quite recently much discussed statue called 'Genesis' exhibits the characteristic features of the disease. It goes astray, however, in one point. The obese stage of the affection, which the figure portrays, is incompatible with either conception or pregnancy.

diabetes; hypertrophy of hands, feet, lower jaw, and tongue; exophthalmos, impaired vision; hypertrophy of the pituitary body, of the pineal gland, of the great sympathetic, of the liver, spleen, and kidneys; atrophy of the heart and arteries." The pituitary tumour was the size of a small hen's egg, had enlarged the fossa, flattened the chiasma, and excavated the sphenoidal lobes.

Case 3.—This was recorded by Cunningham[5] (1879) and named, after Henrot's, "general progressive hypertrophy". Subsequently to Marie's paper, Alexis Thomson[6] described the skeleton and pronounced it to be acromegalic. It was that of a dissecting-room subject who had been in the Royal Infirmary, Edinburgh, for diabetes and who was thus described by his physician, Dr. Muirhead: "The whole aspect and general configuration was so peculiar as at once to arrest the attention of an observant person. His frame was so huge, his movements so ungainly, his expression so unpleasing, his brow so overhanging, and the hands and feet so enormously enlarged as to suggest the idea to some in the ward of a resemblance to a gorilla, and by this epithet he was known amongst the other patients." He was 6 ft. ½ in. high, the circumference of his head was 24½ in., his chest measured 43 in. at the nipple line, and 46 in. three inches below. The pituitary body was as large as a walnut, projected upwards from the expanded fossa, and had hollowed out the base of the brain for its reception.*

FIG. 53.—Richard Dickenson, who died in 1738, aged 68. Probably the earliest case of acromegaly in England of which there is any note. (*From a small picture in the R.C.S. Museum.*)

Case 4.—This was shown by Haddon and Ballance[7] in 1885 as "hypertrophy of the subcutaneous tissue of the face, hands and feet", and published in 1888 as an example of the disease described by Marie. The patient, a woman aged 37, dated her disease to an attack of scarlet fever contracted from her children, and followed by rheumatic swelling of both knees. Her hands began to swell shortly after. The catamenia had ceased permanently a few months before, and a photograph taken just before the scarlet fever showed that her appearance had undergone a striking change. She was a big-featured woman, with broad lower jaw, and thick everted lower lip. The uniform enlargement of both jaws was, apparently, simple hypertrophy. The nasal enlargement was due to hypertrophy of the nasal cartilages and the overlying tissues, the nasal bones being unaffected. The clavicles were larger and thicker than normal and much curved; the hands and feet were gigantic but not deformed, and the subcutaneous fatty tissue was probably disproportionately thickened. In contrast with the hands and feet, the forearms and legs were not enlarged. The speech was guttural and the tongue large, and the right optic disc was atrophied.

* The following observation by Sir Arthur Keith may be quoted here. "I do not for a moment suggest that the Neanderthal race suffered from acromegaly nor that acromegaly is a resurrection of the anthropoid state. From what is known of the function of the pituitary it may be stated with some degree of assurance that all three—the gorilla, the Neanderthal man, and the acromegalic—suffer from that condition known as hyperpituitarism" (*Lancet*, 1911, April 15, 993).

A pituitary tumour had been noted in several of the cases which later on came to be identified with acromegaly, and intracranial changes pointing to pituitary tumour were subsequently found in Marie's second case (Broca[8]), but the importance of this combination was not fully appreciated, the enlargement being looked upon as part of the general hypertrophy. But the constant association of pituitary tumour became steadily more certain, and in 1898 Furnivall[9] showed that in 49 post-mortems on acromegalic cases the pituitary was affected in all, and was enlarged or the seat of tumour in all but two or three. (*Fig.* 54.)

With the discovery of the X rays it soon became possible to recognize an increase in the size of the pituitary fossa during life, and even to trace advancing deformation as the pituitary disease slowly advanced. When it once became clear

FIG. 54.—A pituitary tumour in a case of acromegaly. Messrs. Neal and Shattock's case. A woman, aged 41, in whom the disease had existed for eighteen years, was admitted to Wandsworth Infirmary with well-marked acromegaly, general muscular wasting, loss of power, and very dull mental state. Death from pneumonia. "Histologically the tissue closely resembles that of the anterior glandular lobe of the normal organ." (*Trans. Pathol. Soc.*, 1898, xlix, 224.) (*R.C.S. Museum No.* 48.1.)

than an enlargement of the pituitary body was definitely associated with Marie's syndrome—by which term hypertrophy of the acral parts is generally understood*—attention was naturally focused upon the gland and its functions.

Numerous investigations, both experimental and clinical, have resulted in the accumulation of a great quantity of information, and as knowledge has increased, interest has spread from the pituitary body and infundibulum to that portion of the base of the brain which lies behind the optic chiasma and in front of the cerebral peduncles. This forms the floor of the third ventricle and is often referred to by the somewhat indefinite term 'hypothalamus'.

Giantism.—After Marie's recognition of acromegaly as a distinct affection it was quickly pointed out that similar hypertrophy of the terminal parts occurred in many giants. The preserved skeletons of certain well-known giants were found

* In Cushing's opinion acromegaly should not be diagnosed in the absence of Marie's syndrome.

not only to exhibit enlarged hands, feet, and jaws, but to have enlarged or deformed pituitary fossæ (*Figs.* 55, 56). The connection between giantism and acromegaly could not be doubted, and it was evident that the increase of stature characteristic

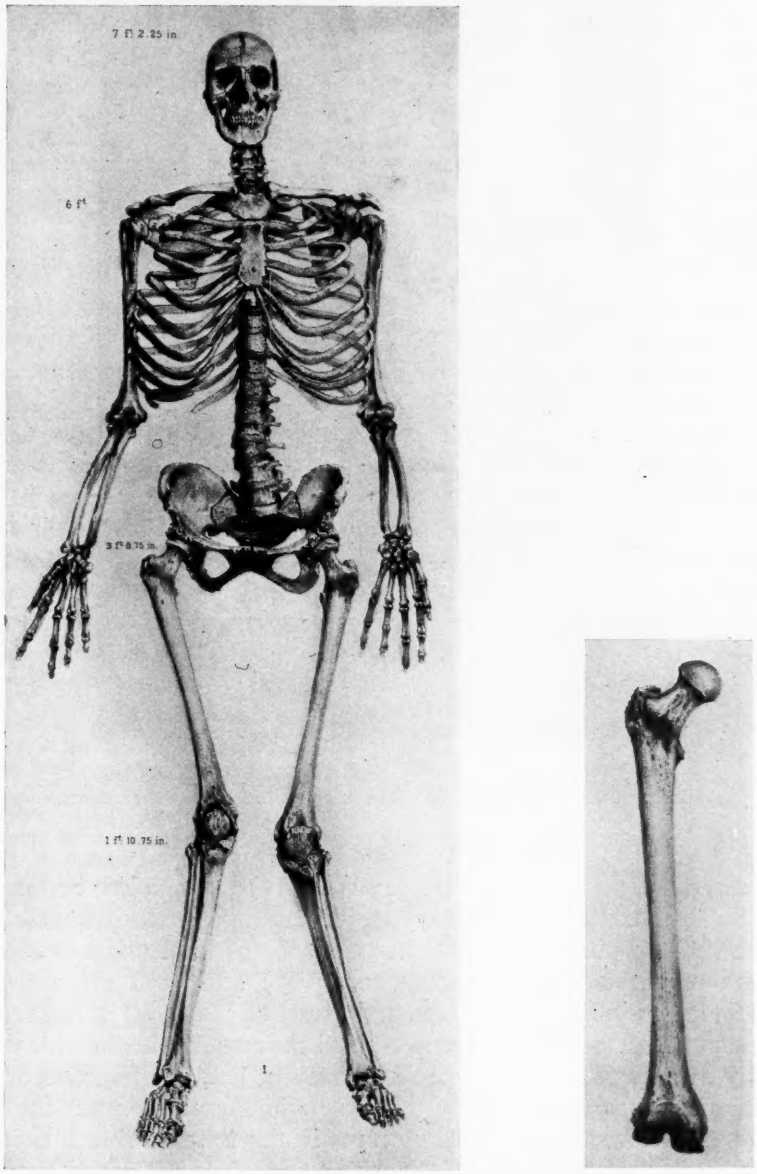


FIG. 55.—The skeleton of Cornelius Magrath, an acromegalic giant. His height was 7 ft. 1⅛ in. His hands were as large as a middling shoulder of mutton, and his shoe last measured 15 in. He was born in 1736 and died in 1775, probably from phthisis. The skeleton is in the Museum of Anatomy and Zoology, Anthropological Section, Trinity College, Dublin. (Cunningham, *Trans. Roy. Irish Acad.*, 1887–92, xxix, 553.)

of the former condition took place in adolescence before the epiphyses became united to the shafts of the long bones. Though acromegalics form a considerable

proportion of all giants, not every giant develops acromegalic characters : 34 recorded giants were enumerated by Sternberg, but only 14 were acromegalics.

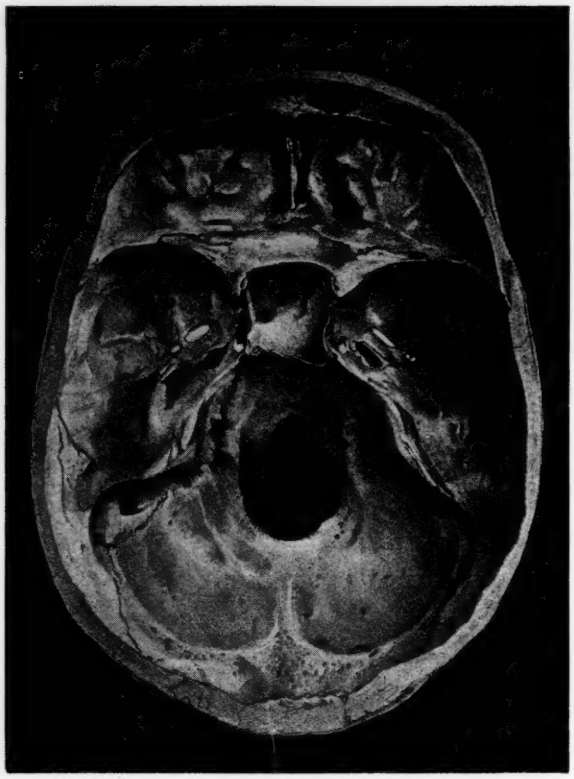


FIG. 56.—The base of Magrath's skull. Note the enlargement of the pituitary fossa, the extent of the frontal sinuses, the hypertrophy of the bones, and the shape of the foramen magnum.

THE CLINICAL FEATURES

The clinical perplexities of acromegaly may be simplified by remembering that: (1) Some of the signs and symptoms depend upon excessive secretion of the anterior lobe of the pituitary; (2) Others may be of local origin, and caused by the pressure of the enlarged pituitary body; (3) It is still undecided whether certain symptoms are of pituitary or cerebral causation; and (4) A few seem to have some relation to other endocrine glands, such as the testicle, the thyroid, the adrenal, and possibly the pancreas. This association may be due to interaction of the ductless glands, or to their activation by the same stimulus that excites the pituitary.

The onset of the disorder usually occurs in the third or fourth decade. It is more common in the third, but it is infrequent in adolescence and particularly so in childhood.* The affection is usually very chronic, and many sufferers live to

* When hyperpituitarism occurs in the very young, it does not necessarily lead to giantism. The explanation is supposed to lie in early union of the epiphyses, and without this all cases of acromegaly stated to have occurred in childhood are, in Cushing's opinion, contestable. F. R. B. Atkinson has collected 32 cases from literature, which occurred between the ages of 6 and 14 years. Of these he rejects 8 as doubtful, and, of the remaining 24, giantism was combined with acromegaly in 6. (*Brit. Jour. Child. Dis.*, 1931, xxviii, 121.)

a good age. Three types have been defined (Sternberg): (1) A benign form which may last as long as 50 years; (2) The ordinary chronic type with a duration of 8 to 30 years; (3) An acute form, which may run its course in 3 or 4 years. Cases in the last group are usually malignant, and only nine were known to have occurred when H. D. Rolleston[10] recorded the following instance:—

Case 5.—A woman aged 35 years was a well-marked case of acromegaly. "Enlargement of the hands dated from the early part of 1894, though the patient had not been well since the birth of a child in 1891. The characteristic skeletal changes were present in addition to advanced double optic atrophy and transient glycosuria." "Death took place in coma on Aug. 16, 1897, after an epileptiform fit, of which she had had several since June, 1897." The post-mortem revealed a soft creamy pituitary tumour, a round-celled sarcoma, which had invaded the base of the brain, the right cavernous sinus, the tip of the petrous bone, damaged both optic tracts, and deeply excavated the sella turcica. From the length of the history the growth may have been a malignant termination of an adenoma—of which, however, there was no evidence.

The distinguishing signs of acromegaly are the great enlargement of the hands and feet, and the remarkable alteration of the face. These changes are so characteristic that acromegalics may often be recognized in the streets; but their onset is so insidious that the sufferer may be unaware of them until his attention is attracted by the increasing size of his gloves, boots, and hat. L. P. Mark,[11] who described his own case, believed his first symptoms occurred when he was 24, but he was 50 before he realized, quite suddenly, that he was an acromegalic, though some of his medical friends had known it for a good many years.

The period antecedent to the development of Marie's syndrome is sometimes comparatively free from symptoms; on the other hand, it may be a time of great distress owing to various subjective discomforts.* In this prodromal stage two

* Dr. Mark's account of his sufferings is interesting. He writes of 'queer feelings' which tended to become more constant and to occur at different times of the day; of an inability to resist cold and exposure, and a liability to cold in the head with abundant rhinorrhœa; of depression of spirits, asthenopia, and an overpowering desire to sleep, to which he would succumb even when sitting upright.

He describes the condition into which he would frequently lapse when this '*acromegalic state*' came on. The 'state' might be merely an uncomfortable feeling or malaise, but in the severe form he would feel very ill, and for a while quite incapacitated. It might last only half an hour or, on his bad days, from morning to night with slight intermissions—probably just after a meal or sleep. When in the 'state' his face became pale, the eyes more sunken, the lids puffy and red, and the lower lip more prominent and drooping. Tears would flow so abundantly that he had to mop his face every few minutes. His hands and feet would perspire and become cold, and he had to change his socks. The acromegalic facies became more decided. The 'state' seemed intimately associated with headache and face-ache. It was not due to fatigue, for it was always worst in the morning. Finally he became depressed by his helplessness and the need to avoid mental or physical effort, and though he could pull himself together by an effort, a corresponding collapse would follow.

For twenty-five years (at the time of writing, 1912[11]) his existence had been a continual fight against this 'state'. It had forced him to regulate his actions to avoid its occurrence at the wrong moment, and it had influenced his life history and his whole mode of life. It reached its climax when he was 38, during a week that he called 'his black week' in which the neuralgia, asthenopia, and nasal catarrh were worse than they had ever been. From that week the intensity of his troubles gradually declined. Fifteen years later, when he had been an acromegalic forty-eight years, he gave an account of the later phases of his case ("Apologia of an Acromegalic", *Med. Press and Circular*, 1927, Oct. 5 and 12). Apparently the disease had stopped. There had been no increase in size in the jaw, the hands, or the feet for ten or twelve years. He had worn his last denture for twenty years, though previously frequent alteration had been necessary to enable his teeth to meet. His heart, eyes, and his headaches were much less troublesome than formerly, but a state of discomfort "which he could only connect locally with the left side of his head occurred now and then."

He adds a note that the subject of Cushing's Case XXV wrote that his case was strikingly parallel to Mark's. Dr. Mark died in 1930 and bequeathed his body to St. Bartholomew's Hospital for scientific investigation.

grave symptoms may make their appearance, viz., *bitemporal headache and impairment of vision.* The former is caused by the pressure of the enlarging gland upon its fibrous envelope, and is relieved when this is split in an operation, or if spontaneous decompression with expansion into the sphenoidal cells takes place. On the other hand, the bitemporal character of the pain is changed to that suggestive of general intracranial pressure if the tumour bursts through the upper coverings and projects into the cranial cavity.

Failure of sight is usually due to primary optic atrophy, which results from pressure of the tumour upon the optic tracts, the chiasma, or the optic nerves. Bitemporal or homonymous hemianopsia is present at some time in many cases, but there is no rule, and one eye may be blind, and the visual field in the other only slightly affected. A choked disc may be grafted upon the atrophy, if the tumour growth has caused a rise of general intracranial pressure. The latter probably depends upon closure of the foramina of Monro and dilatation of the lateral ventricles, and may be associated with an abrupt onset of "increased headache and possibly vomiting".

As the chiasma and tracts are pressed upon only when the pituitary tumour expands upwards, many acromegalics are spared visual disturbance. On the other hand, in cases of primary hypopituitarism marked by infantilism and adiposity in which acromegaly is not present, the optic apparatus frequently suffers seriously.

The diagnostic signs of Marie present the following characters. The enlargement of the *hands and feet* is symmetrical and may be enormous, but those parts are not otherwise deformed. The hypertrophy does not extend above the wrist and ankles, and the forearms and legs are normal. It is easy to realize, even without a radiogram, that the increased size and thickness is only in part due to the bones, and that the skin and subcutaneous tissues take an important share in it. The skin is thick and coarse, and the furrows are deep; the subcutaneous thickening may involve the muscles and by extending between the metacarpal bones may separate them and cause the fingers to diverge.*

Two forms of enlarged hands were described by Marie,[12] the type 'en large', or shoulder-of-mutton hand, when the onset of acromegaly is late (i.e., in adults), and the type 'en long', when it is early. In the latter there is considerable increase in length of the metacarpal bones and phalanges.

Remarkable changes occur in the face. It may assume an elongated oval shape (*see Fig.* 63) due to lengthening of the mandible and the sloping of the forehead caused by expansion of the frontal sinuses; or a square form from hypertrophy of the jaws, malar bones, and zygomatic arches. The orbital ridges, the cheekbones, and the mandible are very prominent, and the overgrowth of the jaws is responsible for a high palate arch, a widening of the mandibular arch, a projection of the chin, and a misfit of the teeth.†

Owing to the prominence of the orbital ridges the *eyes* are apt to be deeply seated, but in some instances they are so prominent that exophthalmos may be

---

* Cases have been reported in which rapid and remarkable diminution of the large extremities has followed extirpation of the pituitary tumour; so rapid may the disappearance be that it is almost certain that some of the enlargement is due to œdema (Cushing's Case XXVI, and Hochenegg's case, *Wien. klin. Woch.*, 1909, 323).

† Mark attributed his indigestion to this misfit, and was greatly relieved by changes in a specially contrived denture from time to time.

said to be present. The latter may be due to hypertrophy of the orbital walls or to changes in the soft tissues of the orbit consequent upon the presence of the intracranial tumour (*see also* p. 81).

The *tongue* is sometimes enlarged to such a degree that it may protrude between the teeth and cause difficulty in speaking, whilst the voice is apt to be harsh and guttural, because the larynx is increased in size and its lining membrane thickened.

The *nose* is large and broad and the skin covering it coarse and thick. The *eyelids* and *lips* are swollen and the lower lip is prominent and everted (*see Fig.* 63).

In addition to Marie's syndrome the increase of the clavicles in length and thickness imparts an unusual breadth to a *chest* which is often enormously enlarged, flattened at the sides, and very deep in the antero-posterior diameter, especially at the lower part. The *spine* commonly presents a cervico-dorsal kyphotic curve, and this may be combined with a lordosis which is probably compensatory.

The examination of the *skull* by the X rays will usually demonstrate some thickening of the cranial vault and considerable enlargement of the air sinuses, especially the frontal and maxillary. As a rule there is more or less alteration of the pituitary fossa, and possibly of its relation to the sphenoidal sinuses. On the other hand, a normal sella turcica may be present when acromegalic signs are marked. A greatly enlarged fossa may be expected when the local signs of tumour are pronounced, but even when they are absent it may be large (*Fig.* 57).

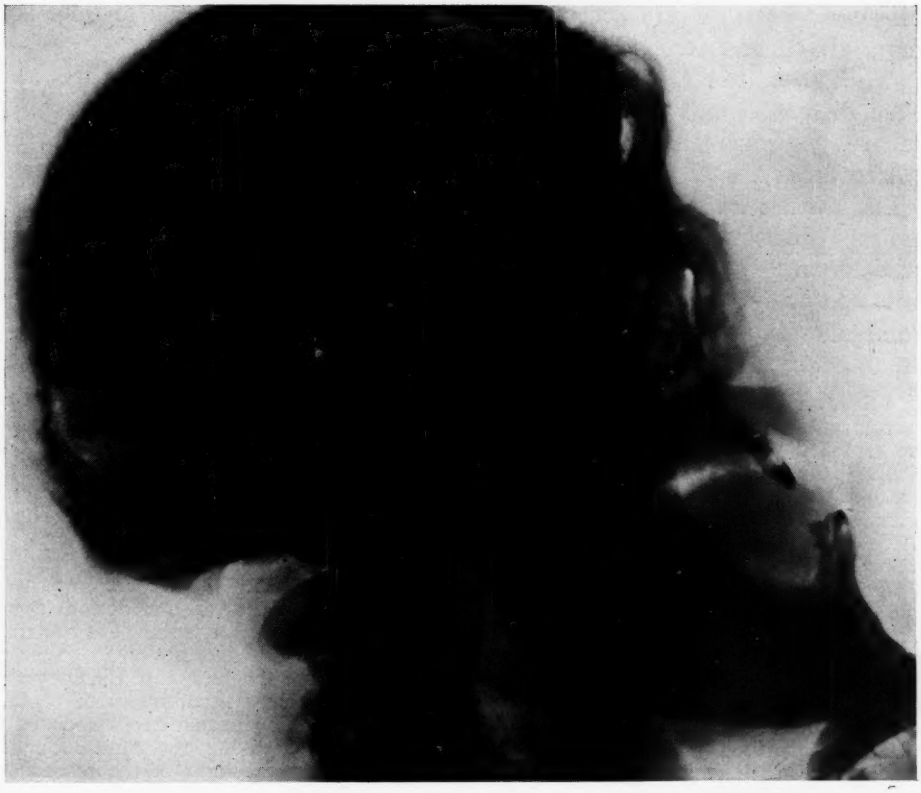


FIG. 57.—Skiagram of the skull of a case of well-marked acromegaly, showing hypertrophy of the cranial vault, enlarged frontal sinus, great enlargement of the pituitary fossa, and prognathous and elongated mandible (*see Fig.* 58). (*Lambeth Hospital records—through the courtesy of Drs. Baly and Stebbing.*)

If allowance is made for the slight magnification that occurs on an X-ray plate, the size of the sella may be gauged from a radiogram; "profile measurements", according to Cushing, "exceeding 15 mm. antero-posteriorly and 10 mm. in depth may be looked upon as indicating enlargement".

The same surgeon has described three different forms of sellar enlargement met with in pituitary affections.

1. The first is confined to cases of acromegaly and giantism *without* adenomatous struma formation. In this form the sellar walls are thickened—an expression probably of the general tendency to bony overgrowth.

2. The second may occur in acromegaly, but is rare unless the hypertrophied gland has become an adenomatous struma. In this variety there is marked thinning and perforation of the floor of the fossa, which may be ballooned and project far into the sphenoidal cells, "the bony capsule being so thin as to cast hardly a perceptible shadow". The changes suggest an advanced stage of the affection when the signs of hyperpituitarism have probably been succeeded by those of hypopituitarism.

3. The third shows "more or less complete absorption of the dorsum, and a downward dislocation of the base, so that the sellar landmarks, with the usual exception of the anterior clinoid processes, are effaced". This form may point to primary glandular tumour which has become malignant and burst its dural capsule, or to an interpeduncular tumour which has eroded the subjacent sphenoid.

The changes in the fossa revealed by the X rays are important not only from a diagnostic point of view, but because they may help the surgeon to infer active tumour growth if successive films show increasing destruction.

The So-called Hypopituitary Syndrome.—Sooner or later in the course of the disease certain significant symptoms develop to which the term 'hypopituitary syndrome' has been given. They are: (1) Failure of strength, etc.; (2) A tendency for the patient to put on fat; (3) A high degree of sugar tolerance; (4) The loss of sexual desire and power; and in some cases a transient or permanent polyuria (diabetes insipidus). Some of these symptoms deserve a fuller consideration.*

Adiposity.—There is a tendency to the eventual deposition of fat in all acromegalics and giants, just as there is in eunuchs and in myxœdema; but the

---

* Sainton and State (*Rev. neurol.*, 1900, viii, 302) have pointed out that in some cases of acromegaly there is a good deal of pain ("la forme douloureux d'acromegalie"), and they have arranged the various forms of pain that occur into the following groups: (1) Osteo-articular pains, many of which are apparently associated with the increase of growth; (2) Neuralgic pains; (3) Muscular pains—cramps; (4) Pains resembling tabetic crises; (5) Extremity pains—acroparæsthesia. These groups fall into two classes: (1) The rheumatoid type forms which constitute the pains of onset; and (2) Those that depend upon some alteration in the peripheral or central nervous system, 'the hyperalgique type'. The latter are *signs of the cachectic period of the malady.* In a case in which muscular cramps were a prominent symptom they found osseous plaques in the D.M. (spinal) with calcareous granules on its inner surface and a cord lesion chiefly affecting the columns of Goll. They attributed the pains to mechanical pressure of the nerve-roots by the calcareous plates.

Sternberg (*Ibid.*, p. 37) refers to several cases (Henrot's, Duchesnan's, Linsmayer's) in which the arachnoid contained either strongly marked or many small plates of chalk. A somewhat similar condition is described by J. H. Sheldon in an unusual case associated with acromegalic giantism (*Brit. Jour. Surg.*, 1929, xvi, 405). Though Sternberg did not consider this condition as having any pathological significance, yet in the light of the researches of Leriche and Policard (*Les Problèmes de la Physiologie normale et pathologique des Os*) on the nature of ossification it is quite probable that in acromegaly it is associated with the excessive bone absorption of the later stages, and therefore it may be directly connected with the affection.

hypophysial type of adiposity is the common one (Cushing). Possibly in all three it is connected with deficient secretion of the ductless gland specially concerned, i.e., the pituitary in acromegalics, the testes in eunuchs, and the thyroid in the myxœdematous. The fat in acromegalic cases is evenly distributed (*Fig.* 58), but is not limited to the subcutaneous tissue. Fatty masses may form about the viscera, and their substance even may be invaded; in the liver especially there is often extensive replacement of the cells by fat globules.

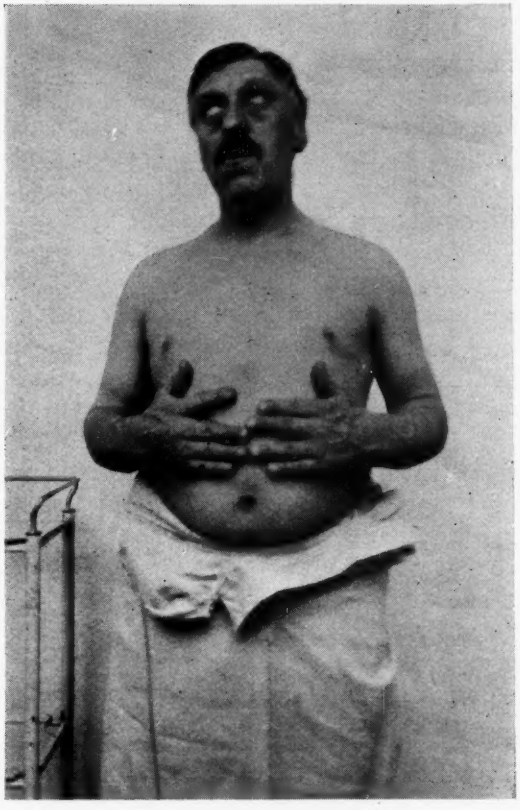


FIG. 58.—Photograph of a well-marked case of acromegaly in a late stage. A. C., aged 40. There was a history of fifteen years' duration of the disease, of numbness in the hands followed by Marie's syndrome, of headaches, double optic atrophy and blindness, some adiposity, and towards the end uncinate symptoms, anosmia and loss of taste. (*By the kindness of Dr. Stebbing.*)

The accumulation of fat is usually associated with an ability to assimilate excessive amounts of sugar, but the quantity reaching the blood is markedly subnormal (hypoglycæmia). It is practically certain that most of the sugar is converted into fat, and that sugar metabolism is largely in abeyance (Cushing's experiments).

The syndrome—adiposity, high sugar-tolerance, subnormal temperature, slowed pulse, asthenia, and drowsiness—has been attributed to a deficiency of the posterior lobe secretion.* The secretion of this lobe is thought to contain a hormone essential to carbohydrate metabolism, and it can easily be obstructed by various intracranial lesions. The emaciation,

---

*Compare hibernation, with its low rate of metabolism, and its possible relation to seasonal pituitary variations.

"There can be little doubt that in the greater number of cases" of acromegaly "as the malady progresses, glandular insufficiency supervenes." Cushing's studies in carbohydrate tolerance show that "in acromegaly the individual's capacity to assimilate sugars progresses from a state in which carbohydrates are rapidly metabolized to one in which they are merely stored; in other words, from a state in which there is either a low assimilation limit or an actual hyperglycæmia with glycosuria, to one in which alimentary glycosuria is difficult or impossible to elicit. This would appear to be the strongest argument in favour of the transitional character of the disease from hyper- to hypo-pituitarism on which such great emphasis has been laid throughout this study."

"The transition doubtless may occur at the stage of the malady before the skeletal manifestations of hyperpituitarism have become outspoken, and thus the acromegalic changes may be inconspicuous (e.g., Case XII); or it may occur after the characteristic fixed bony changes have become full blown (e.g., Case XXVIII); or it may possibly not occur at all, and the disease may run a self-limited course after a stage of hyperpituitarism, with the restoration of a fairly normal glandular activity (e.g., Case XXXI)." (Cushing, *The Pituitary Body and its Disorders*, p. 251. The cases are Cushing's.)

spontaneous glycosuria with hyperglycæmia, and slight elevation of temperature which follow posterior lobe administration are in favour of this theory.

Glycosuria is so common at some time or other in acromegaly and giantism that according to Marie it is met with in one-third or one-half of all cases. It is probably connected with increased functional activity of the pituitary, but it is also suggested that it may have a cerebral (*see* p. 100) or a pancreatic origin. Falta[13] inclines to the latter theory because pancreatic atrophy has been noted in some cases. When the glycosuria occurs late in the disease, as in Mark's case, its hyperpituitary causation must be very doubtful.

Loss of Sexual Desire and Virility.—These are believed to indicate that the active or hyperpituitary stage of acromegaly has passed or is on the wane. Similar symptoms occur in other pituitary affections besides acromegaly, and in all they may be associated with atrophy of the testes. The interrelation of the pituitary and the testis will be apparent if the testicular functions are studied in conjunction with certain symptoms met with in the different pituitary affections.

Of the two functions of the testis, one—*the reproductive*—depends on the formation of spermatozoa in the seminiferous tubules, the other on the formation of a *supposed internal secretion* responsible for the secondary sexual changes that mark the onset of puberty. This internal secretion is believed to be produced by certain cells, known as the interstitial cells of Leydig, present in the intertubular connective tissue. Each function may develop alone, and when both have developed normally it is possible for recession to occur. The bearing of these facts both on acromegaly and on other pituitary disorders was illustrated by Cushing from cases reported in *The Pituitary Body and its Disorders*, and epitomized here :—

Case XLVII (Loc. cit., p. 224).—A boy, aged 8 years, acquired secondary sexual characteristics at 6—viz., masculine voice, axillary and pubic hair, and over-development of the genitalia. At 8 he was overgrown (5 ft. 6 in.), adipose, and blind. At the time of an exploratory cranial operation a small portion of the testis was removed for microscopical examination. The interstitial cells of Leydig were in excess, but the tubules were of pre-adolescent type, and without spermatozoa.

Case VIII (Loc. cit., pp. 63, 277).—A man, aged 41 years, "had never fully acquired the secondary characters of sex. He had a feminine type of adiposity and hirsuties, and so on; nevertheless he had been sexually active. His testis showed fully developed tubular epithelium with spermatozoa, but there was a paucity of interstitial cells, none of which could be identified as cells of Leydig."

Case XXXII (Loc. cit., pp. 162, 277).—A giant, aged 36 and 8 ft. 3 in. high, presented the acromegalic peculiarities and had reached the stage of dyspituitarism. There was adiposity, increased carbohydrate tolerance, a childish voice, absence of axillary and pubic hair and of beard, small genitalia, atrophic testes, and he was impotent. Both spermatozoa and Leydig's cells were absent from the testis.

These cases are accompanied by confirmatory photomicrographs from sections of the testes in each.

The phenomena pointing to retrogression in adult acromegalics in whom the secondary sexual manifestations have already developed are less pronounced. Still, in the majority of cases the patient becomes aware of diminished sexual desire and of impotence. This feature is the more noticeable because in the early stage of hyperpituitarism an increase in sexual inclination is usually present. The transition may be illustrated by Cushing's Case I.

Case I (Loc. cit., p. 30).—A man, aged 35 years (December, 1910), was, at the age of 19, 6 ft. 4 in. high and of unusual strength. His habits were good except for an uncontrolled sexual desire. At 23 he had polyuria; at 27 attacks of bursting frontal headache and pains in the extremities, followed by copious discharge of shiny mucus, which gave relief for days or weeks. Acromegaly was diagnosed at this time. In 1907 it had been noticed that his features were changing and that he was getting large all over. Polyuria without glycosuria was present, also weakness and drowsiness. He easily tired, and there was complete loss of sexual desire and power.

There can hardly be a doubt that the *amenorrhœa* of acromegalic women is to be explained in much the same way as loss of virility in men. The amenorrhœa of the declared disease is not difficult to understand, whether the theory of a deficient posterior lobe secretion is adopted, or a more recent hypothesis of pressure upon the basophil cells of the anterior lobe (*see* p. 99) as a cause of such deficiency is preferred. But why amenorrhœa should be the first symptom to mark the onset of the disorder is not very clear.

Pluriglandular Syndromes.—In addition to the signs which point to a derangement of the testicular functions in acromegaly, there are occasionally present, in some cases, symptoms which suggest that the secretions of certain of the other endocrine organs may be disturbed simultaneously with that of the pituitary. Of these, sweats, palpitations, nervous irritability, voracious hunger, tremor, and exophthalmos may be connected with over-activity either of the thyroid or the pituitary, but opinion hesitates as to which of the two glands is responsible. Reference has already been made (p. 77) to one explanation of exophthalmos, whilst Cushing attributes it to blood stasis from local pressure on the intracranial venous sinuses, and points out that it is present in almost all cases of tumour, and is rare in the absence of definite growth.

But the *thyroid* is undoubtedly affected in many acromegalics. In the 29 cases mentioned by Furnivall there were only 5 normal thyroids; of the others, 17 were hypertrophied, and 7 showed degenerative changes. Cushing had rather a different experience: in 15 cases, in all of which there were signs of pituitary insufficiency, the microscope showed only excess of colloid and a low epithelium (functional involution). There had been no symptoms of hyperthyroidism in any of these cases, though possibly a hypersecretory stage of thyroid secretion might have passed unnoticed.

There is no doubt that thyroid deficiency is the cause of myxœdema when that condition is present in acromegaly, for it is relieved by thyroid and not pituitary tablets. In two cases of Hochenegg's the thyroids became permanently enlarged after extirpation of the pituitary, and after experimental extirpation of the pituitary definite changes, viz., cellular desquamation and hyperplasia, have been found in the thyroid (Cushing). It has been suggested that enlargement, such as occurred in Hochenegg's cases, may point to the thyroid assuming a compensatory rôle, which, as both the pituitary and the thyroid exercise an influence on bone growth (e.g., cretinism), is at least plausible.

Some clinical facts, however, give the impression that the same cause may excite both glands to over-action; thus Falta's Case 30 developed a goitre simultaneously with acromegalic signs; eventually Basedow's disease gave way to myxœdema. But Falta points out that myxœdema may also develop without signs of hyperthyroidism.

In some cases symptoms such as hairiness and pigmentation raise the question of implication of the *adrenals*. The following is an example (Cushing):—

Case XXV.—A Hebrew, aged 40, had been developing acromegaly for six years. There was no adiposity, but an unusual degree of hypertrichosis. The coarse skin was mottled everywhere with a remarkable brownish pigmentation. Carbohydrate tolerance was not increased (limit for glucose 150 grm.). The thyroid was slightly enlarged and the testes were apparently unaffected. Cushing remarks of this case that "it represents a fairly recent and still active condition of hyperpituitarism. The extreme hypertrichosis* and excessive sweating were notable features. . . . The case serves as a fair clinical illustration of the pluriglandular nature of the malady. . . . In this patient furthermore there was an exceedingly low blood-pressure. This, with the pigmentation, hirsuties, and muscular weakness, suggested adrenal involvement."

It must be admitted that the above facts justify no very definite conclusions, but taken in conjunction with P. E. Smith's experiments and the observations of Cushing and Davidoff in the Rockefeller Monograph No. 22 they indicate a connection which future research will no doubt make plainer.

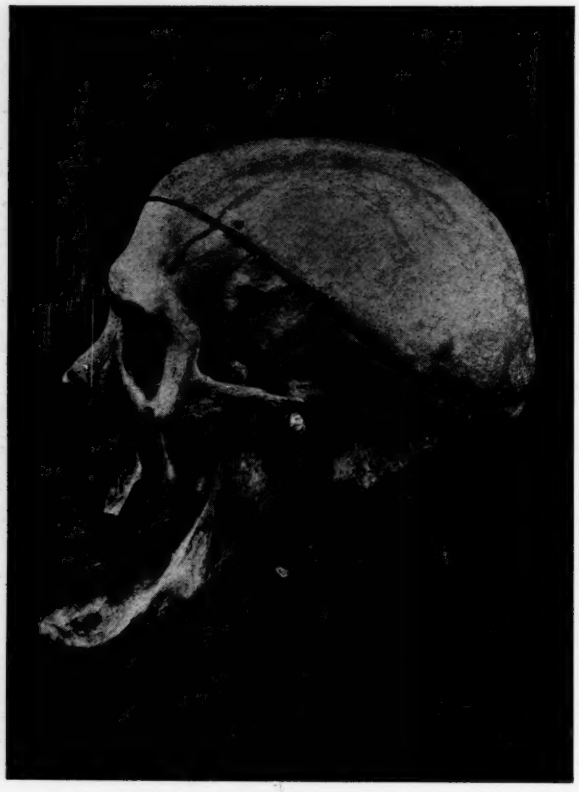


FIG. 59.—Lateral view of the Greenwich (acromegalic) skull. (*R.C.S. Stores.*)

THE BONE CHANGES AND THEIR PATHOLOGY

The process of ossification is normal, but the skeletal changes result from its exaggeration, and are almost certainly induced by an excess of the anterior lobe

* Falta looks upon abnormal hairiness in acromegalics as an accentuated secondary sexual manifestation. (Loc. cit., p. 248.)

secretion. The uneven distribution of these changes may be explained by the influence of pressure and traction upon osteoblasts rendered hypersensitive by the hormone secreted by the anterior pituitary lobe. "Wherever there is traction applied by ligaments or by muscles, or pressure applied as in standing or walking, growth takes place in that part of the skeleton where the various forms of force act" (Keith[14]). A student making a not very critical inspection of an acromegalic skeleton might easily take it for one of a normal individual, unless, perchance, he got a lateral view, when he would be struck by the great depth of the chest, and the prognathous lower jaw (*Fig.* 59), provided these features were at all marked. But the difference between an acromegalic skeleton and a normal one becomes apparent when the measurements of corresponding parts are compared.

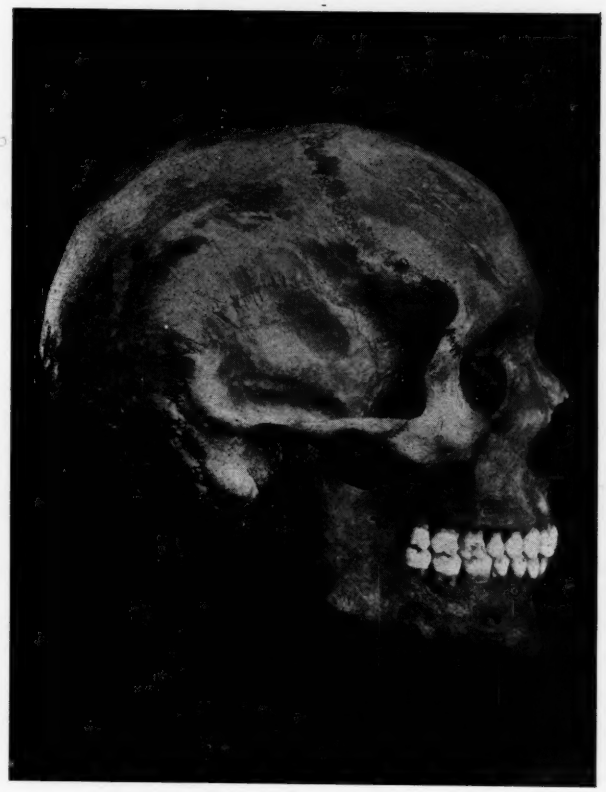


FIG. 60.—Side view of a normal skull. (*R.C.S. Museum.*)

In the following table the measurements from the skull of a pronounced case of acromegaly (Dr. Corner's case, R.C.S. Museum, No. 3860.1) are contrasted with those from a normal Englishman's skull and with those of the skull of a man 6 ft. 3 in. in height in which the pituitary fossa was normal (Sir James Cantlie's specimen, R.C.S. Museum). (*Figs.* 60, 61.)

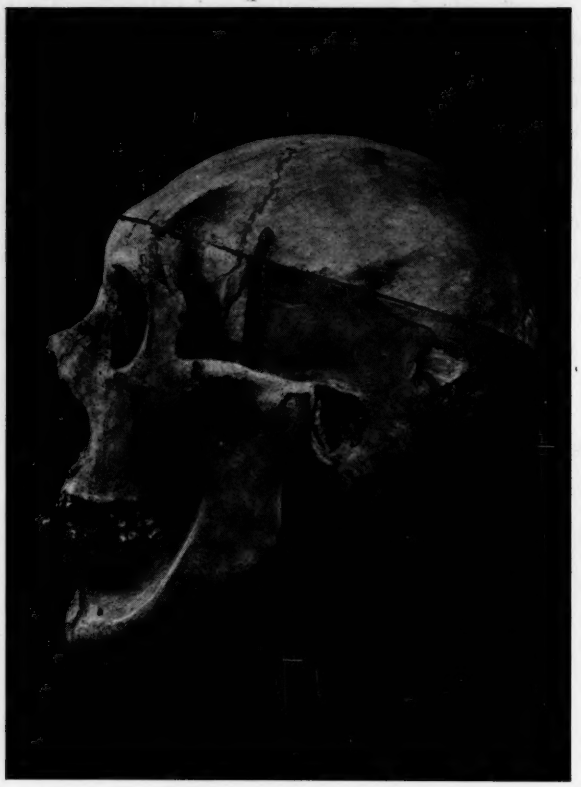


FIG. 61.—Skull of a case of acromegaly. Dr. Corner's case. Patient was a man aged 42, who had marked signs of the disease at 25 years of age. Height, 6 ft. ½ in. He was bedridden for his last ten and a half years. Some months before death there was improvement in intelligence, speech, and sight, which last had been seriously impaired. His hands and fingers became less (? spontaneous decompression into the sphenoidal cells—*see Fig.* 57). His bowels were relieved with great difficulty every seven days, and the rectum (preserved) is enormously enlarged and thickened, but is not a part of a general intestinal hypertrophy. The lungs were greatly enlarged, but there had been no lung affection at any time. (*R.C.S. Museum*, No. 3860.1.) *See also Figs.* 63, 67, 69, 70, 71, 73.

	ACROMEGALIC	NORMAL ENGLISHMAN	MAN 6 FT. 3 IN. HIGH
	Inches	Inches	Inches
1. From the root of the nose to the tip of the chin ..	7	5	5
2. Lateral oblique measurement; from the mid-point of the interparietal suture to the chin (tip) ..	11½	10	11
3. Circumference of skull ..	23½	21¾	22¼
4. Superior maxilla: orbital margin to alveolar margin	2⅜	1⅝	
5. Superior maxilla: width of palate area—between the last molars	1¾	1⅝	2
6. Length of hard palate* ..	2¾	2	1⅞
7. Mandible: depth of body	2	1¼	1¼
8. Mandible: width of arch between last molars ..	2⅜	2	2⅛
9. Zygoma, length from the tubercle to the posterior vertical border of malar bone	R. 2⅝ L. 2½	2⅛ 2	2¼ 2¼

* According to Keith's observations the palatal area in the acromegalic is not increased.

In the following account of the changes which distinguish the individual bones in acromegaly, Sir Arthur Keith's explanatory description of those in the skull will be largely followed.

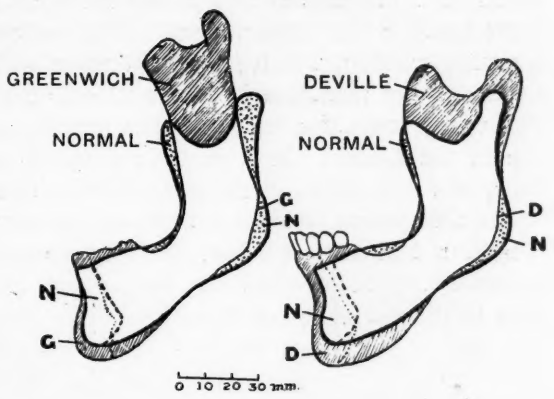


FIG. 62.—The normal and acromegalic mandible contrasted. The shaded areas mark deposited new bone. The stippled areas mark where bone has been absorbed. The thick outline represents the normal mandible. Sections of the symphyses are indicated by the dotted or interrupted lines. N, Normal; G, The Greenwich skull; D, The Deville skull. (*By the courtesy of Sir Arthur Keith, 'The Lancet'* 1911, April 15, 996.)

The Jaws (*Fig.* 62).—The alterations in the maxillæ and mandible are responsible for one of the most distinctive features of the affection. The heaping up of porous vascular bone on the alveolar margins increases the length of the face, raises the vault of the hard palate and the dental sockets, and separates the teeth.* This alveolar hypertrophy is to be attributed to the stimulation of bone growth by the intermittent pressure of mastication. The underhung and projecting lower jaw and chin, so characteristic of acromegaly, is explained by the changes that take place in the mandible. Besides the alveolar overgrowth, additional bone is deposited on the mental eminence and on the lower margin anterior to the groove for the facial artery. But the most interesting changes take place in the ramus, which becomes narrower and increased in height, sometimes more than one inch.

FIG. 63.—Cast of the face of Dr. Corner's case. (*R.C.S. Museum*, No. 3860.1.)

Absorption takes place in the region of the angle, producing the appearance of an opening out of the angle between the body and the ramus. The increase in height is due to growth taking place at the upper end. The condyle, the coronoid process, and the sigmoid notch form the growing portion, and pressure on the condyle, and traction on the coronoid process and

* Separation of the teeth is produced by elevation of the sockets; it is not due to an increased length of alveolar margin. The latter depends on the number and size of the teeth.

the notch constitute the stimulus to growth. By the growth at the joint the mandible is pushed downwards and forwards, and a misfit between the upper and lower teeth is the consequence. The narrowing of the ramus is explained by muscular traction, which is exerted more and more in the line of the ascending ramus, as the mandible is elongated and depressed by the growth at the joint. The wider separation of the angles may in part be connected with the increased size of the tongue. It is brought about by absorption on the inner side of the bone, and deposition on the outer side. The absorption and deposition of bone is like that which fashions a bone in ordinary growth, and they involve both the cancellous and cortical tissue. At first the new bone is porous, but later becomes condensed. Only occasionally, and in some places, does the bone deposit approximate to the inflammatory type.*

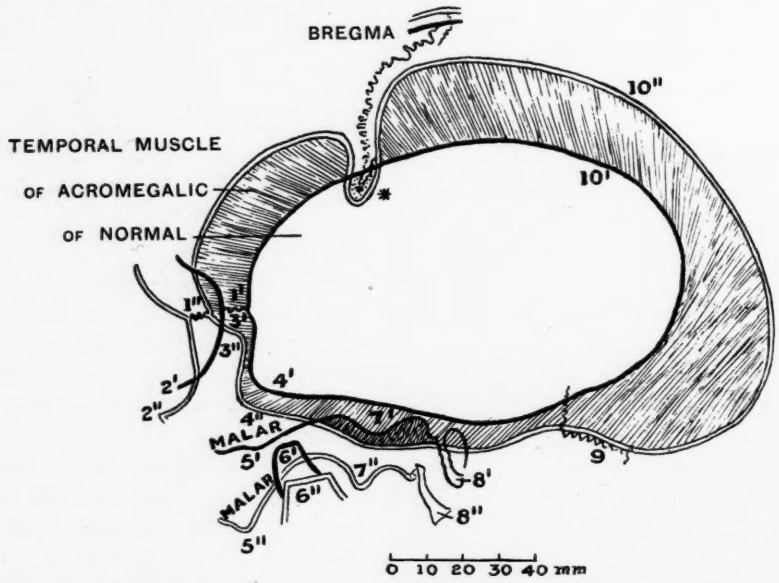


FIG. 64.—Comparison of the normal origin of the temporal muscle and boundaries of the temporal fossa with those of the acromegalic. 1′ External angular process of the normal skull; 1″ Of the acromegalic; 2′, 2″ Lower margin of orbit; 3′, 3″ Ascending process of the malar bone; 4′, 4″ Upper margin of the zygoma; 5′, 5″ Origin of the masseter (lower margin of malar); 6′, 6″ Coronoid process; 7′, 7″ Articular eminence; 8′, 8″ Tympanic plate; 9′ Parieto-mastoid suture; 10′, 10″ Temporal ridge (muscular). * Stephanion. (*By the courtesy of Sir Arthur Keith, 'The Lancet', 1911, April 15.*)

The Face (*Fig.* 63).—The study of the facial alterations must begin with the growth changes that occur in the temporal fossa and temporal muscle in the normal child. These are continued and exaggerated in acromegaly. As the attachment of the temporal muscle grows upwards, backwards, and forwards the temporal ridge

* Similar changes occur in some other conditions, but they are very rare. The following instances may be cited; (1) Hypertrophy of the right half of the lower jaw reminiscent of the acromegalic deformity is seen in Sir Jonathan Hutchinson's specimen from Mr. J. E. Adams' case of "Osteomata on the Interior of the Cranium and Nasal Fossa" (R.C.S. Museum, No. 1362.2, *Trans. Pathol. Soc. Lond.*, 1871, xxii, 204). (2) A cast in the R.C.S. Museum (No. 38.2) illustrates Mr. Barwell's case of a boy aged 7, in whom there was congenital hypertrophy of the bones of the right side of the face. The hypertrophy of the jaw was strictly limited to the right half. The soft parts and the right half of the tongue shared in the hypertrophy (*Trans. Pathol. Soc. Lond.*, 1881, xxxii, 282).

recedes. The key to the overgrowth of the supra-orbital ridges, and to the expansion of the frontal sinuses in acromegaly lies in the anterior region of this advancement and recession, i.e., in the displacement forwards of the anterior part of the temporal ridge. The abnormal temporal development produces a forward growth of the outer orbital region. "The external angular process with the ascending malar process comes to

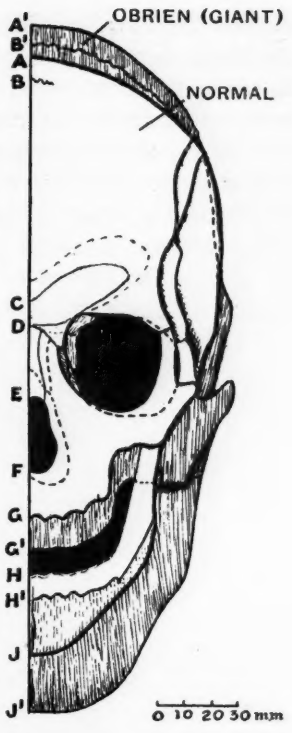


FIG. 65.—Half the full face of an acromegalic (the giant O'Brien) compared with the normal. A, Highest point of vault above the plane of orientation (subcerebral plane), normal; A', Highest point of vault above the plane of orientation (subcerebral plane), O'Brien; B, Bregma, normal; B', O'Brien; C, Glabella; D, Nasion; E, Tip of nose; F, Nasal spine; G, Alveolar point, normal; G', Ditto, O'Brien; H, Alveolar point of lower jaw, normal; H', Ditto, O'Brien; J, Mental eminence, normal; J', Ditto, O'Brien. (*By the courtesy of Sir Arthur Keith, 'The Lancet', 1911, April 15.*)

occupy a position 10 to 15 mm. further forwards and downwards than in the normal skull", with the result that the zygoma is lowered, the height of the temporal fossa is increased, and the external auditory meatus is depressed—in some cases 10 mm. or more. (*Fig.* 64.) Again, the supra-orbital overgrowth displaces the root of the nose forwards and downwards, so the nose appears to be long. It is also conspicuous, as the overgrown

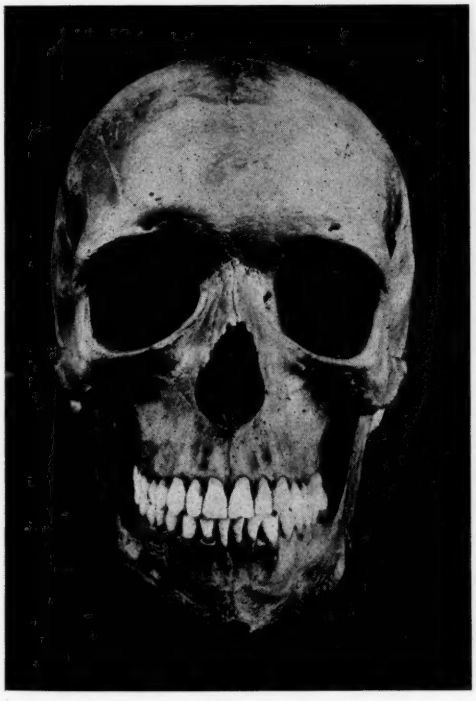


FIG. 66.—Front view of a normal skull. (*R.C.S. Museum.*)

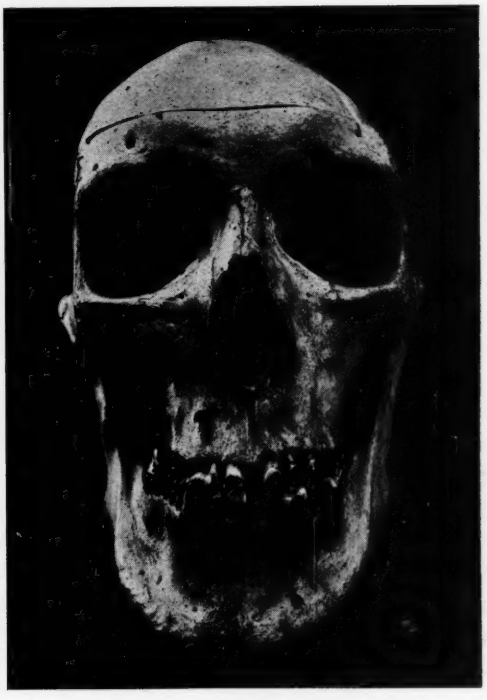


FIG. 67.—Front view of an acromegalic skull. Dr. Corner's case. (*R.C.S. Museum, No.* 3860.1.)

supra-orbital region predominates over the maxillary part of the face which is not projected more than usual. The increase in the face-length in a well-marked case is about 20 mm.; that of the upper face (10 to 17 mm.) being chiefly due to the increase in depth of the alveolar margin of the maxilla. (*Fig.* 65.)

In the front view two alterations call for notice. The first concerns the orbit, whose outer wall is moved forwards and outwards so that the orbits are enlarged outwards and downwards. The second is the remarkable enlargement of the malar and zygoma, the depth of the body of the former being increased as much as 8 to 15 mm. The orbital enlargement is a consequence of the temporal changes, and that of the malar and zygoma of the traction exerted by the masseter. (*Figs.* 66, 67.)

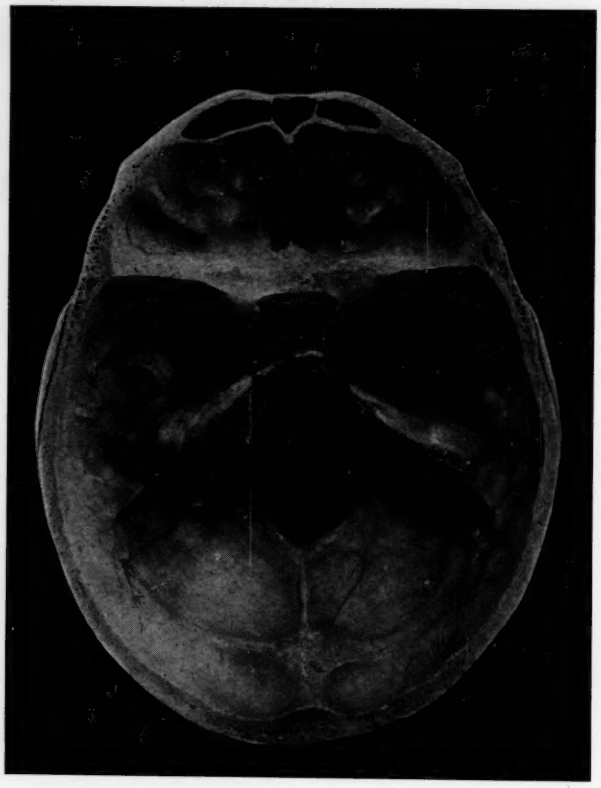


FIG. 68.—The base of a normal cranium. (*Osteological Collection, R.C.S. Museum.*)

The Cranium (*Figs.* 68, 69, 78–80).—The modifications of the vault are not nearly so distinctive as those of the jaws, the supra-orbital ridges, and the face. Its thickness varies a good deal. Beadles[15] has recorded the case of an insane woman aged 40 years in whom the cranial vault was remarkable for its thinness and its large frontal sinuses (*see Fig.* 79). Most acromegalic calvaria are thicker than normal, and in rare instances they may be so thick as to resemble the vault in osteitis deformans (*see Fig.* 80). In some cases both tables are defined, but in others they cannot be differentiated from the dense diploë.

The frontal bone is the first part to be affected and undergoes the greatest amount of change, and in many there is a tendency to the formation of small dense

osteomata on its inner table. Posteriorly, the superior curved line with the occipital protuberance is moved upwards from 8 to 10 mm., and the distance between the mastoid processes is increased from 10 to 25 millimetres. Both these changes are due to the increased area of attachment of the neck muscles.

The Base.—The foramen magnum is displaced backwards in giants and forwards in adult acromegalics, a peculiarity explained by the increased length of the basilar process in the former and its atrophy in the latter. The occipital condyles may be reduced in size and their axes altered, so that the head is carried in increased

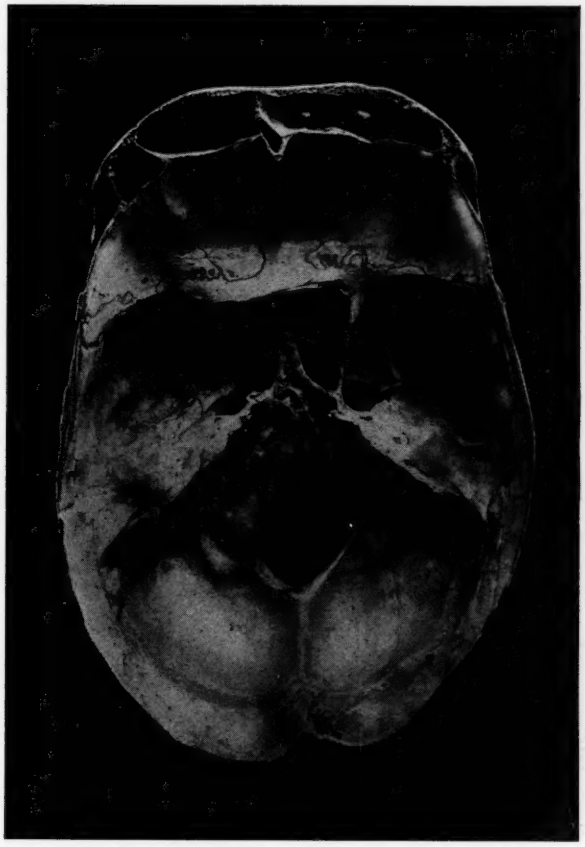


FIG. 69.—Base of an acromegalic cranium showing erosion and deformation of the pituitary fossa and its vicinity; expansion of the frontal sinuses, atrophy of the basi-occipital, and alteration of the foramen magnum. Dr. Corner's case. (*R.C.S. Museum*, No. 3860.1.)

extension. In some cases they may be pressed upwards more into the skull, as if the base had been softened. In Dr. Corner's case they are surrounded by considerable lipping, and in one of the Greenwich skulls (R.C.S.) (*see Fig.* 78) an atrophied axis is ankylosed to the occipital bone.

The Pituitary Fossa.—In nearly all cases there is some enlargement of the sella. In some it is inconsiderable, and occasionally it does not exceed normal limits; but in others the fossa is much increased in size, and in the worst examples the landmarks may be lost in the irregular cavitation of the sphenoid caused by tumour erosion. (Cushing's three types have been described on p. 78).

All the veins in and below the base dilate, especially the emissary veins. The small venous foramina open out, and one of them, the cranio-pharyngeal canal, may become patent.* The cranial capacity may be slightly increased, but the evidence on this point is inconclusive. That of the giant O'Brien (R.C.S. Museum) is only 10 c.c. more than the mean of a normal English skull.

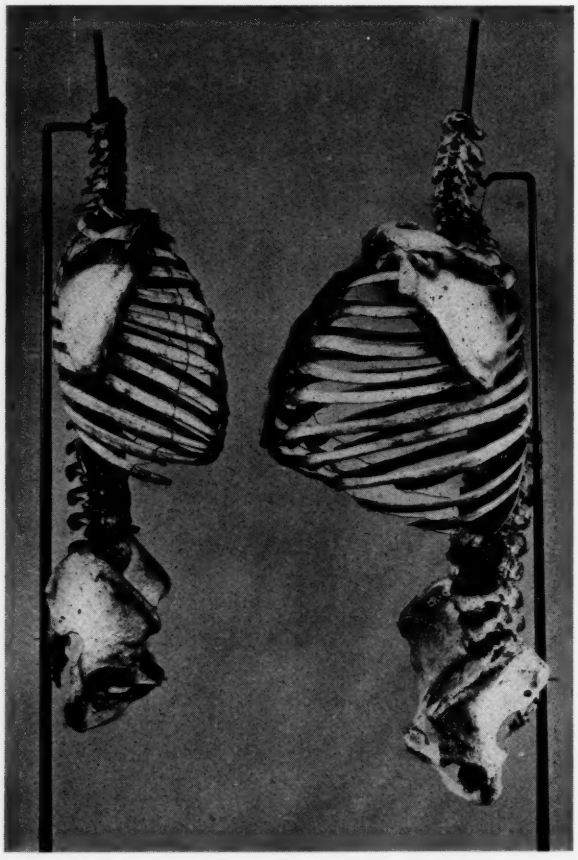


FIG. 70.—A normal, and an acromegalic thorax viewed from the side. A, Normal; B, Acromegalic. Dr. Corner's case. (*R.C.S. Museum, No.* 3860.1.)

The Thorax and Shoulder Girdle (*Figs.* 70–72).—The great size of the chest is very striking. It is largely due to the increased length of the ribs, especially of the middle ones, which carry the lower part of the sternum unduly forward. Its width is emphasized by the over-long clavicles. These points are well brought out in the illustrations, but will be even better appreciated from the comparative measurements (Dr. Corner's case).

* Keith points out that in anthropoids it remains open and that it is present in O'Brien, in other giants, and in many acromegalics, but he explains it by a dilatation of a normal minute vascular channel and not as a congenital persistence betokening an inherent defect in the pituitary.

	Acromegalic	Normal Englishman	Man 6 ft. 3 in. high (R.C.S.)
	Inches	Inches	Inches
Circumference of thorax over inferior angles of scapulæ and 4th rib	45	33	36
Length of clavicle	8	6¼	6⅜
Length of ribs (5th and 7th, R. and L.)	17½	13	14
Width of 1st rib (R. and L.)	1⅜	⅞	1
Depth of chest, xiphoid to spine	9⅜	6½	6¾
Transverse diameter above 6th rib	13½	9	9½

The ribs are unusually wide and the increase in their length is much greater than any seen in other long bones (excluding giantism). The length-growth is determined by several factors, viz., the permanence of the costal cartilages which

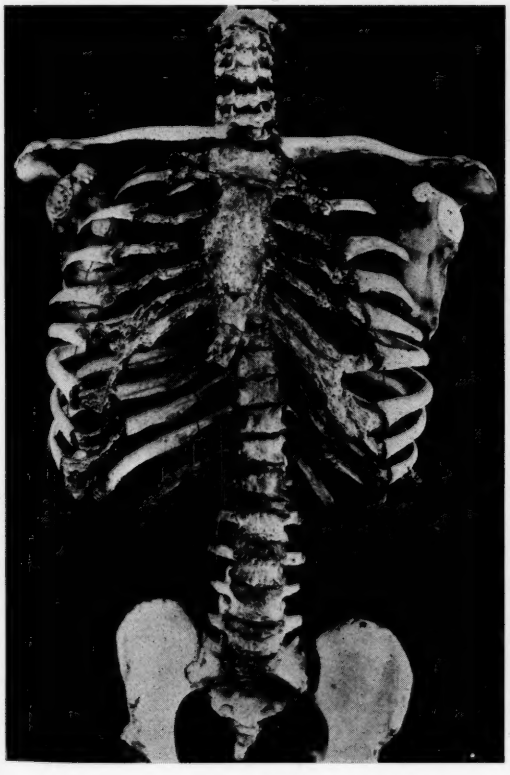


Fig. 71.

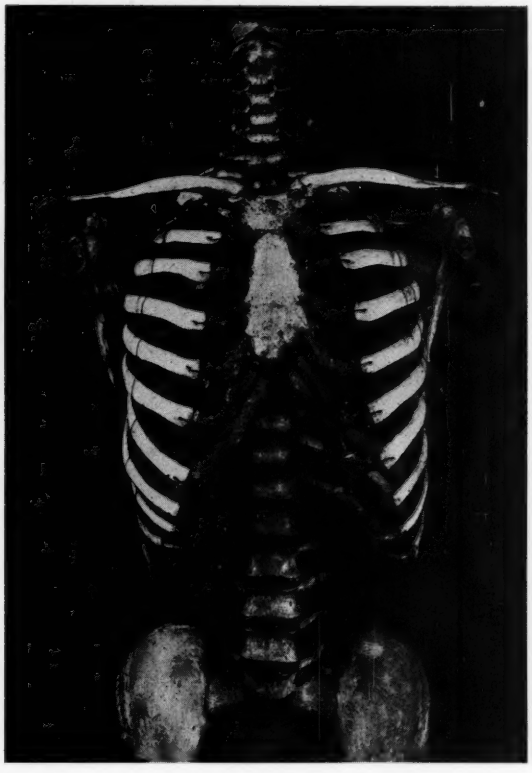


Fig. 72.

Figs. 71, 72.—Front views of thorax and spine. *Fig.* 71, Acromegalic. Dr. Corner's case (*R.C.S. Museum, No.* 3860.1). *Fig.* 72, Normal.

are elongated, hypertrophied, and irregularly calcified, the exaggerated growth processes, *and, last but not least, the hypertrophy of the lungs.* Their increased width

is due to the traction of the intercostal and chest muscles. The cartilages appear to penetrate the ends of the ribs, which are slightly expanded as if to receive their articulating portions. At this point, microscopically, a young layer of bone lies over the growing cartilage.*

The clavicles are rounded, thicker, less curved, and longer than usual, and the muscular grooves and ridges are abnormally developed. The increased growth in length is often remarkable, and no doubt partly the result of traction at their outer ends, called into play by the outward pressure of the expanding thorax.

FIG. 73.—The skeleton of an acromegalic foot. Dr. Corner's case. (*R.C.S. Museum*, No. 3860.1.)

The Long Bones.—Apart from the clavicles and ribs, the long bones may not differ very obviously from normal ones. The shafts are usually smooth and formed of compact bone, though they may be pitted and marked by vascular foramina and impressions. The articular ends are apt to be notably more massive and less elegantly modelled than usual. The rough areas and ridges associated with muscular and ligamentous attachments—such as the linea aspera, deltoid tubercle, etc.—are commonly exaggerated, and may, like the articular margins, be beset with small bony excrescences and rugosities. In many cases where there is no question of giantism the limb bones are not only thicker and more massive but may be increased in length—especially the humerus and femur. Nor is it difficult to understand this increased length-growth and massive bone-ends, even when the epiphysial lines have long been closed, if it is appreciated that growth can be determined in acromegaly by pressure and traction (compare the mandible).

The Bones of the Hand and Foot (*Fig.* 73).—The metacarpals, metatarsals, and the phalanges are not much altered. Sometimes their length is increased (Marie's long hand), but instead of being elongated they may be thick, rounded and massive, and the attachments of the aponeurotic flexor sheaths marked by sharp hypertrophied ridges. Small lateral exostoses on the shafts may be present, and the articular ends frequently show hyperostosis and lipping, suggestive of osteo-arthritis, a condition that not infrequently complicates the main affection.

---

* A very full account of the histology of the rib cartilage in the normal subject and in acromegaly, with the changes occurring at the chondro-costal junction, is given by Erdheim, "Die Lebenvorgänge im normalen Knorpel und seine Wucherung bei Akromegalie". There are a number of illustrations.

A costal cartilage grows from its periphery (perichondrium) towards its central axis. The zone of proliferating cartilage lies parallel to the long axis of the cartilage, and not transversely as in the epiphyses of the long bones. A calcified layer is not developed on the deep or central border of the proliferating zone, but the vitality at this part begins to wane and the cartilage dies. The central core of a rib cartilage is composed of dead tissue.

The Vertebral Column.—The hypertrophic changes in the vertebræ may in some instances be of an osteo-arthritic nature, but Erdheim,[16] who has carefully investigated them, believes that there is a *true acromegalic spondylitis.* He points out that the changes affect the dorsal region in greatest measure, and tail off in the cervical and lumbar regions. They are due to the deposit of new periosteal bone upon *the diaphyses*—a deposit which is thickest in front, diminishes at the sides till it disappears, and is absent in the spinal canal. The margins of this partial bone sheath are fissured, so that a row of tooth-like processes appears above and below a vertebral disc. The overgrowth considerably increases the antero-posterior diameter of the body, and, if looked at from above, its shape is in marked contrast with that of a corresponding normal or osteo-arthritic vertebra.

In osteo-arthritis, on the other hand, the hypertrophic changes occur at the edge of what represents *the epiphyses* and are more irregular in their distribution (osteophytes). When exuberant they give a waist-like appearance to the diaphysis in which the surface of the normal body is exposed covered only by the periosteum.

Kyphosis; *Flat-foot.*—A cervico-dorsal kyphosis (spondylitis muscularis) and flat-foot are frequent concomitants of acromegaly. They are no doubt chiefly due to the failure of muscular tone and power which characterize its later stages. Atrophic changes in the vertebræ may be a factor, but deterioration of the muscular power is probably the main one.

Acromegalic Arthritis.—Erdheim's[17] researches show that a specific form of arthritis may occur in acromegaly. He points out that in osteo-arthritis the changes in the articular cartilage depend on degeneration. They begin at the surface, and extend deeply until the cartilage may be completely destroyed. In

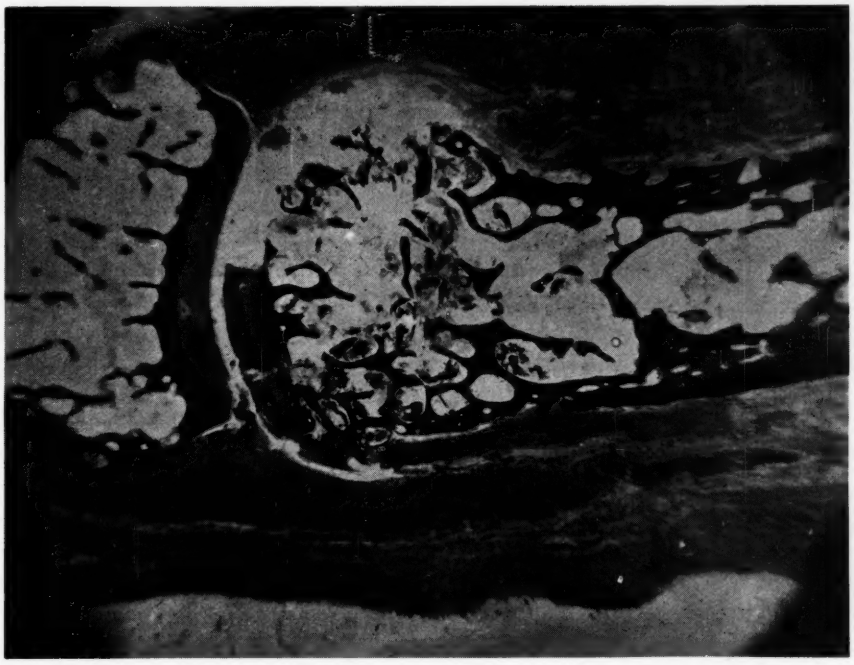


FIG. 74.—Section of a phalangeal joint and adjacent portions of the phalanges from an acromegalic old man (70 to 80 years). Showing the atrophic changes in the bone. (× 4.)

acromegaly the exact opposite occurs. The changes result from exaggerated proliferation starting in the proliferation zone in the deep layers of the cartilage. As the proliferating focus advances towards the surface, its overlying normal cartilage is thinned by the pressure, and softened by the proximity, of the proliferating tissue. The covering layer is worn through by friction and the proliferating nodule or focus exposed. The edges of the ulcer are at first undermined, for crevices form between the passive and the proliferating cartilage as the latter increases. The presence of this undermined edge is characteristic of the acromegalic ulcer of articular cartilage, and when it disappears owing to the continued rubbing, it is very difficult to distinguish the acromegalic from an osteo-arthritic lesion.

FIG. 75.—The anterior half of the right femur of an acromegalic giantess of 26½ years (height 7 ft. 8½ in.). To show the atrophy of the cancellous and cortical bone. (*Through the courtesy of Professor Brash.*)

Bone Atrophy.—Not only does absorption go hand in hand with bone growth in the evolution of the bony changes, but in the later stages of the disease, bone atrophy may be marked and extensive (*Fig.* 74). Evidence of this can be seen in skulls (*see Fig.* 79) and in the vertebræ (*see Fig.* 71, in which osteo-arthritis is present); but it may proceed to such lengths that a long bone may be converted into a cylinder of compact tissue with almost complete disappearance of the cancellous structure (*Fig.* 75).

Histology of the Process of Ossification.—The most helpful account is that of Marie and Marinesco,[18] who state that there is no essential difference from normal ossification. The proliferated cartilage cells, however, are arranged in irregular groups instead of columns, and these groups are separated by a considerable width of matrix. The line of junction of the cartilage and bone is festooned and irregular. The medullary spaces are rich in vessels and young cells, and vascular cell buds advance from them into the calcified matrix between the cell groups. The cell groups open into the spaces, and primary medullary spaces are formed, upon whose boundaries laminated bone is laid down by apposition of osteoblasts. In the diaphysis of the bone examined (middle phalanx of the great toe) resorption was going on, but osteoclasts on the trabeculæ were rare.

Under the periosteum, both layers of which are thickened, fresh layers of bone are produced, but they are disposed more irregularly than usual. The periosteal fibres play the same rôle as the calcified cartilage between the cell groups, i.e., as directing strands for ossification.

The marrow in the later stages is often fatty, as might be expected, but Hunter,[19] in a man who died from cerebral hæmorrhage in the fifth year of his acromegaly, has described increased vascularity of the marrow and cancellous tissue of some of the long bones, and markedly red diploë in the cranial bones; whilst in the bones adjoining the pituitary fossa the marrow was of a deep plum colour; moreover, there were hæmorrhages in the medullary tissue of the tibia and the femur. The pituitary was enlarged, highly vascular, and red, in marked contrast to a normal pituitary. These changes were no doubt associated with active hyperpituitarism.

PATHOLOGY OF THE CHANGES IN THE SOFT TISSUES OF THE ACROMEGALIC PARTS

The soft tissues of a great toe were also investigated by Marie and Marinesco[18] (*Fig.* 76).

In the skin the various layers of the epidermis were thickened, the papillæ enlarged and elongated, and the derma proper was remarkably hypertrophied. Its thickness was 150 mm., whereas in portions of normal skin it measured from 0·5 to 0·7 mm. It was composed of thick bundles of connective tissue with hypertrophied fibres running parallel to the axis of the bone, and others obliquely and perpendicularly to the bundles. On its deep surface its vessels were thickened by cells concentrically arranged.

The adipose layer of the subcutaneous tissue was loaded with fat, and the connective tissue strands radiating from the aponeurosis and periosteum were two or three times thicker and more numerous than usual. The vessels were sclerosed, and in some the internal coat was so hypertrophied as to narrow the lumen.

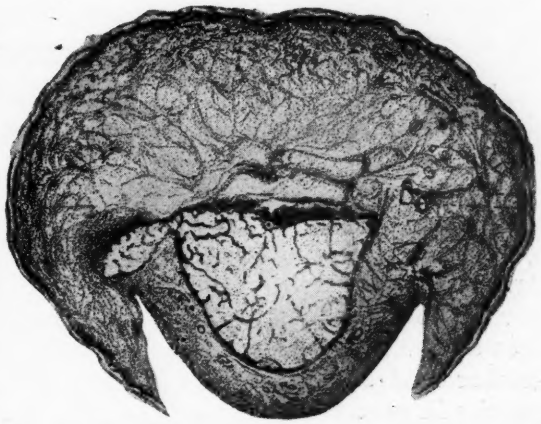


FIG. 76.—Transverse section of an acromegalic great toe showing: thickened epidermis; dermis excessively hypertrophied, and composed of thick bundles of connective tissue; thickened Malpighian layer; hypertrophied strands of connective tissue which radiate towards the deep face of the dermis; walls of vessels thickened; thickened periosteum; enlarged medullary spaces. (× 2.) (*After Marie and Marinesco, "Arch. de Med. exper.", Fig.* 6, p. 545.)

The small nerve-sheaths were hypertrophied, the septa between the nerve-bundles thickened, and in the nerve-fibres the nuclei of the sheath of Schwann were multiplied, and many had lost their myelin. There was both peri- and endoneuritis. The peripheral nerve and vascular changes, as a rule, occurred only in the parts affected with acromegaly.

Hypertrophy is also met with in the *cranial, spinal, and sympathetic nerves.* Thus in Henrot's case the pneumogastrics, the glossopharyngeals, and the brachial plexuses were notably increased in size, and a life-sized drawing testifies to the remarkable enlargement of the main sympathetic system, with its ganglia and branches.

SPLANCHNOMEGALY

Cushing and Davidoff,[20] from observations made from forty-four completely recorded autopsies, "infer that the tendency to a disproportionate and widespread enlargement of the viscera is generally speaking a definite characteristic of the disease". The one exception is the brain, whose weight is ordinarily within normal limits. Cunningham's[5] case is a good example. The liver weighed $7\frac{3}{4}$ lb., more than twice its usual weight; the kidneys were nearly three times the ordinary weight and apparently quite healthy; the spleen weighed 14 oz. The stomach and intestines had attained a wonderful capacity; the former was four to five times the size of the ordinary stomach; the small intestine, when inflated, measured

37 ft. 3 in. in length, and the large intestine 11 ft. ½ in. The whole intestine from pylorus to anus was little less than twice as long as in the ordinary male subject. Other well-known cases in which splanchnomegaly was present are Henrot's (liver, spleen, kidneys, and sympathetic system) and Neal's (liver, spleen, kidneys, heart, and thyroid). The hypertrophy frequently involves only some of the organs. In Dr. Corner's case there was marked hypertrophy of the lungs, in which there was no emphysema. The overgrowth had evidently been subjected to considerable restraint by the enlarged and capacious thorax. A most unusual and deep moat-like sulcus encircled the upper lobes just below the apices, a proof of sustained expanding pressure against the first ribs (*see* p. 91).

PATHOGENESIS

The pathogenesis of acromegaly and giantism is closely connected with the physiological functions of the cells that compose the anterior lobe of the pituitary body.

In the normal pituitary the anterior lobe is surrounded by a connective-tissue capsule, and columns or masses of cells are separated into variously shaped alveoli by connective-tissue strands, supporting blood-vessels. (Dean Lewis—Bohn and Davidoff[21]). The cells are not all alike, and can be differentiated by their peculiar reactions to different stains. One kind, known as *chromophobes*, does not stain with eosin or osmic acid, but takes only a slight yellowish tint. These cells are small. Another kind consists of large coarsely granular cells, styled *chromophils*. The granules in some take up an acid and in others a basic stain. These cells used to be classified, according to their reaction to eosin and hæmatoxylin, into acidophils and basophils; but as the acid and basic dye theory proved faulty, Dott and Bailey[22] preferred to use a non-committal designation for the stained granules. To the eosinophilic granules which stain with eosin, acid fuchsin, neutral dyes, etc., they applied the term '*alpha granules*', and to the basophilic granules, which stain with alum hæmatoxylin, kreso-fuchsin, acid-violet, etc., the term '*beta granules*'.*

The two kinds of chromophil cells are distributed indiscriminately about the gland, but the cells of the pars tuberalis, which constitute the stalk, are mostly basophils. According to one view, there is really only one kind of anterior lobe cell, the different types marking different functional stages. Benda[23] thought he was able "to follow satisfactorily the transitional changes from the empty chromophobe to the loaded eosinophil", and "that the *small* cells with few granules represented the indifferent embryonal forms capable of multiplying, and that the accumulation of granules in the dark cells (eosinophil) indicated the highest point of functional activity; and that, finally, the *large cells* with few granules resulted from a temporary or permanent cessation of function." On the other hand, it is suggested that the three types are quite independent.

As a result of experimental and clinical observations Cushing has ascribed a definite function to each variety of the chromophil cells: to the acidophil,

* "Many synonyms exist for these cell types in accordance with theories of their staining reactions, or the varying views regarding their function. (1) Chromophobes—chief cells, reserve cells, siderophils, etc. (2) Chromophils: (*a*) Eosinophil—acidophil, fuchsinophil, oxyphil, etc. (*b*) Basophil—cyanophil, etc." (Dott and Bailey).

undoubted association with growth, and to the basophil a probable and intimate relation to the organs of reproduction and sex. He thinks that these vital functions are activated by separate hormones, which arise in the different forms of chromophil cells.

The Acidophil Cells.—These are specially associated with acromegaly and giantism. The enlargements of the anterior pituitary lobe found in these diseases show a large excess of acidophil cells which are grouped into considerable masses to form an adenomatous tumour (Schafer[24]).*

This association is supported by certain very suggestive facts :—

1. Partial extirpation of such an adenomatous tumour has been followed in many cases by rapid amelioration of the symptoms ; and in one case (Hochenegg's) gradual diminution in size of the enlarged extremities set in and complete cure eventually resulted.

2. In young animals growth is checked when the anterior lobe is removed.

3. Giantism has been produced in a rat by repeated injections (parenteral) of saline emulsion of fresh bovine anterior lobe tissue (Evans and Long, 1921[25]).

The following account of the *histology of acromegaly* has been given by Dean Lewis.[26] The patient from whom the material was obtained was a man of 46 who died from cerebral mischief unconnected with his acromegaly. For nearly seven years his feet, hands, and head had been gradually getting larger, but post mortem the pituitary was not noticeably enlarged. There was, however, a notable hyperplasia of the chromophil cells. These rested directly upon the endothelial walls of the capillaries instead of on connective-tissue strands which support the blood-vessels and normally limit the alveoli. The cells were irregularly grouped in the inter-capillary spaces. Lewis describes two kinds of chromophil cells. The granules of the predominant cells—large polyhedral cells (*Fig.* 77)—stained best with iron hæmatoxylin (acidophils). Very few chromophobes and cyanophil (basophil-hæmatoxylin) cells were found, and they were grouped about the boundary zone between the nervous and glandular lobes. He regarded the great excess of highly functioning chromophil elements, their irregular distribution, and the lessened amount of stroma, as indicating excess of function, and he came to the conclusion that this cell hyperplasia was the fundamental change in acromegaly, because he had seen similar appearances in other acromegalic cases, and they were not present in several pituitary glands taken without discrimination from different cases.

The absence of pituitary enlargement, as in Lewis's case, is not very common in acromegaly—more often the gland is increased in size and assumes the tumour formation, especially in those that call for operative interference. Bailey and Cushing,[27] who examined a large number of pituitary tumours (from 100

---

* *Pregnancy cells.*—Probably not unconnected with the ' acidophil cells ' are certain large granular or fibrillated acidophil cells (siderophil—*σίδηρος*, iron), which have been observed during pregnancy to form masses within the pars anterior. This is always enlarged at those times. They have been termed ' pregnancy cells ', and after parturition they diminish in size and lose their specific appearance (Schafer).

" *The chromophil adenoma.* The eosinophilic tumour. This adenoma is the form which accompanies the hyperpituitary syndrome. . . . As a rule these adenomata are of the strumous variety with scant connective tissue, and they are prone to cystic degeneration. In our experience tumours of this type are constantly associated with the syndrome of overgrowth, i.e., acromegaly or giantism." (Dott and Bailey : material from 39 cases was examined.)

consecutive cases, which included others besides acromegaly), made further valuable observations. They described six different histological types :—

1. In this type practically all the cells were packed with alpha granules.

2. Most of the cells contained large numbers of alpha granules.

3. Only a ring of alpha granules occupied the periphery of a variable number of cells.

4, 5, and 6. No alpha granules were present.

When they compared these types with the clinical conditions connected with them, it was found that the highly acidophilic adenomata (1 and 2) were *always*, and the pure chromophobe adenomata (4, 5, 6) *never*, associated with acromegaly (if two doubtful cases in type 4 were excepted). In the third or intermediary

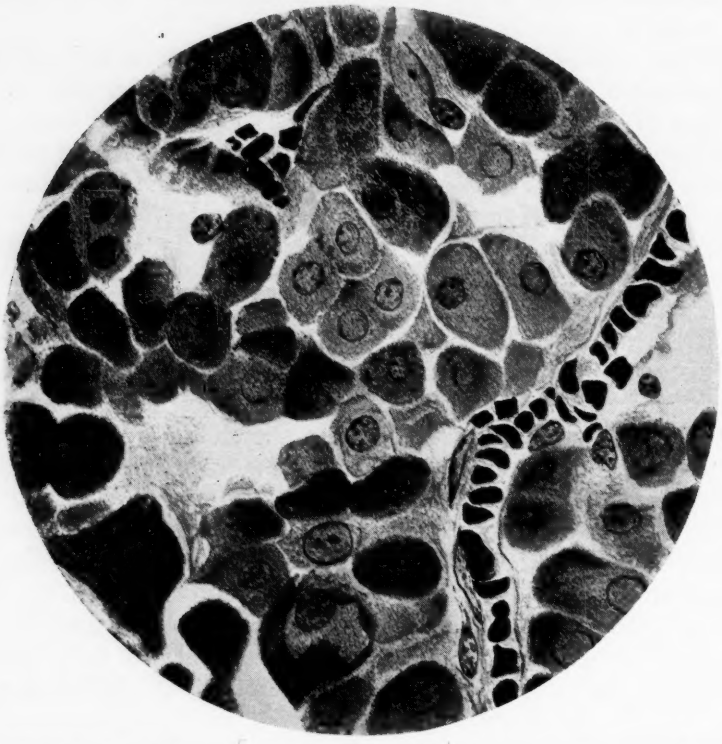


FIG. 77.—Portion of a section cut from the pituitary body of a case of acromegaly. Stained with iron hæmotoxylin (Leitz Obj. 12, Ocular No. 4). *(By the courtesy of Dr. Dean Lewis.)*

type, in which sparsely disposed cells contained a peripheral zone of alpha granules, clinical evidence of a fugitive hyperpituitary reaction was apt to be present; the microscopical appearances* were characteristic of a class of case in which there was a synchronous development of the acromegalic and hypopituitary syndromes. Thirteen such cases from 162 verified adenomata were classified by Dott and Bailey as belonging to a 'mixed type' with dyspituitary syndrome. Bailey and

* Dott and Bailey[22] give four coloured drawings illustrating: (*a*) The normal histological appearance of the anterior lobe; (*b*) Crowded 'alpha' granules (Nos. 1 and 2); (*c*) Chromophobe adenoma (Nos. 4, 5, 6); (*d*) Adenoma with mixed clinical syndrome—cells outlined by a ring of 'alpha' granules (No. 3).

Cushing christened this clinical condition belonging to the third or intermediary type '*fugitive acromegaly*'.

The Basophil Cells.—These are thought, by those who advocate this theory, to secrete a hormone capable of activating the reproductive organs. This belief is based upon the following facts. The results of experiments seem to justify the presumption that the increased lustfulness, and the exaggeration of the secondary sexual characters such as hairiness, seen in the hyperpituitary stage of acromegaly, may depend upon the basophil cells of the anterior lobe (Engle,[28], Teel[29]). That an active sex substance exists was shown by Zondek and Aschheim,[30] who demonstrated its presence in the urine during pregnancy; and at the autopsy of a case with exaggerated sexual characters Teel found a small basophil adenoma of the pituitary—till then an unknown form of pituitary tumour.[25]

Again, certain circumstances suggest that the secretion of the sex hormone may be interfered with by pressure upon the basophil cells. Thus, suprasellar lesions producing a chiasmal injury with little or no enlargement of the fossa may be due to several kinds of tumour, one of which is the chromophobe type of pituitary tumour. In such cases the function of the anterior lobe is not interfered with, and no amenorrhœa results. But if a growing chromophobe tumour is confined within the sella, amenorrhœa invariably occurs. The same effect is no doubt produced by a *chromophilic* tumour in acromegaly, for the sex function is definitely interrupted when the pituitary fossa is greatly expanded by intrasellar pressure (Henderson[25]). On the other hand, "partial extirpation either of a chromophobe or an acidophilic adenoma in women" may result in the resumption of normal menstruation, and even in the occurrence of child-bearing.

Though it may be stated with some confidence that acromegaly depends upon the circulation of an excessive secretion of a growth hormone resulting from a hyperplasia of the acidophil cells of the anterior lobe, there is, at the present time, a clash of experimental evidence as to the seat of the influence that controls the sexual functions, notwithstanding the arguments pointing to the basophil cells. It has been located by Camus and Roussy,[31] whose results were confirmed by Bailey and Bremer,[32] in a group of nuclear masses in the tuber cinereum. They found that extirpation of the pituitary *in a dog* did not cause atrophy of the external genitals if the brain was not damaged, and, further, that after extirpation sexual vigour was preserved, and pregnancy was followed by the birth of living pups, which the bitch suckled for several days. On the other hand, genital atrophy, or at least arrest of development and loss of sexual appetite, resulted from experimental lesions of the base of the brain.

The inference from these results was qualified by those of P. E. Smith,[33] whose hypophysectomized *rats** showed pronounced retrogression and atrophy of all the reproductive organs; and as these parts were restored by replacement therapy (daily pituitary transplants) he concluded that the atrophy was due to the removal of the anterior lobe, and not to brain injury.

Adiposity, High Sugar Tolerance, and Polyuria.—These have been attributed to a deficiency of the posterior lobe secretion, probably resulting from

---

* Owing to the similar disposition of the dural diaphragm in rats and man, in whom it is only perforated for the passage of the stalk, the gland below, and the nerve structure above, can be separately subjected to experimental injury.

atrophy of that lobe from the pressure of the pituitary tumour, or from obstruction to the outflow of the secretion owing to compression of the stalk. Doubts, however, arose when Ashner[34] suggested that the polyurias, glycosurias, adiposity, and general atrophy that followed extirpation of the pituitary in dogs might be caused by incidental damage to the tuberal nerve centres; and the doubt was increased when, in the light of their experimental results, Camus and Roussy concluded that these symptoms were in all probability the result of injury to the adjacent nerve centres in the floor of the third ventricle, and these comprised a group of nuclear masses believed to control the metabolic and sexual functions in the normal animal.

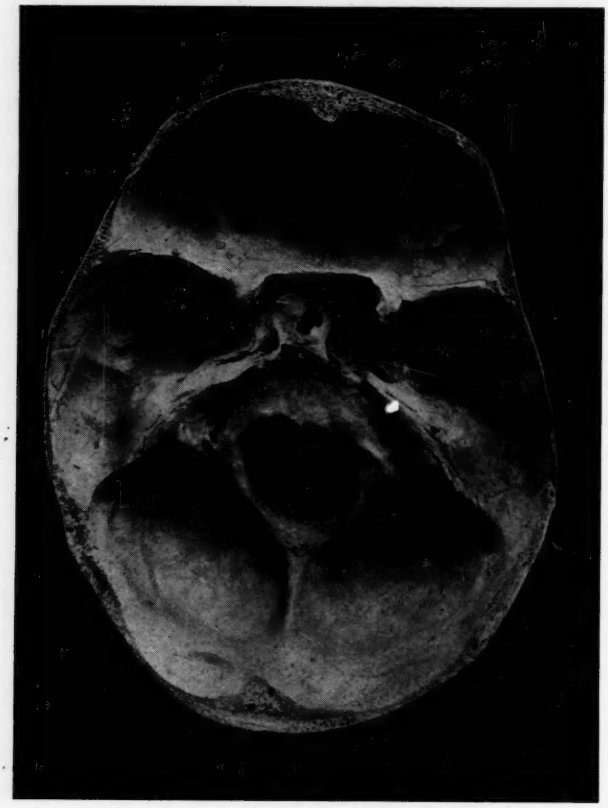


FIG. 78.—Base of the Greenwich (acromegalic) skull. Compare with *Fig.* 69. Note the exostoses on the internal table and the different shape of the foramen magnum. (*R.C.S. Stores.*)

Important evidence in support of this view was furnished by the work of Richter and of P. E. Smith. The former produced a persistent polyuria in a series of animals by a carefully placed stab-wound through the bases of rats' skulls just anterior to the pituitary, and the latter contrasted two experimental procedures. In one, by the ventral route, he extirpated the pituitary by negative pressure (suction), easily permitted by its anatomical disposition in the rat, and in the other, using the temporal approach, he injected chromic acid into it. In the latter experiment the caustic effects might be expected to extend beyond the limits of the pituitary body. The symptoms that followed were similar except as regards

obesity. The rats in which the chromic acid method was used developed an early and unusually marked adiposity, whilst those in which the pituitary had been removed showed none or only a slight obesity after five or more months.

These researches have cast considerable doubt upon the 'hypopituitary syndrome' theory, and Cushing admits that they have badly shaken "our accepted views of the relation of these symptoms (polyuria, adiposity, sexual dystrophy) to the pituitary body itself". In the Lister Memorial Lecture Cushing gives the impression that he has in his mind the idea that eventually it may not be impossible to harmonize to some extent the contradictory results of the different experimenters, and that deficiency symptoms may prove in some cases to be caused by interference with nerve-fibres which run from the supra-optic and paraventricular nuclei down the stalk to ramify in the posterior lobe round the secretory islands, or possibly by damage to the blood-supply to the gland as it passes along the infundibulum.

Changes in the Thyroid and Adrenals.—In both sets of Smith's experiments there invariably resulted atrophy or involution of the thyroid, and retrogressive changes in the cortex of the adrenals. The nature of the changes in the various ductless glands has been carefully discussed by Cushing and Davidoff in the Rockefeller Monograph No. 22, to which the interested reader is referred. They conclude their study of the thyroid with the following sentence: "We may, nevertheless, safely say that hyperpituitarism in its acromegalic guise tends to enlarge the thyroid disproportionately to the other tissues, and that this enlargement proves, histologically, in the large majority of cases, to be the type of the inactive gland familiar in the colloid goitre." Concerning the adrenals, they say, "evidently hypertrophy of the adrenal cortex, with or without the formation of adenomata, is one of the most constant expressions of hyperpituitarism."

ETIOLOGY

What is the cause of the excessive secretion of the anterior pituitary lobe which is thought to be the effective factor in the production of acromegaly? It is not certainly known, but it is conceivable that the increased secretion may be due to abnormal stimulation or abnormal sensitiveness of the gland. The excitant may possibly be a hormone originating in some physiological process, or a toxin connected with some bacterial infection. Its origin may be still more complicated, and the following considerations may have some relation to the problem.

Pregnancy.—During pregnancy the pituitary body increases in weight and size, and changes from a greyish-red colour to white. It subsides after parturition, and involution is complete at the end of lactation. With a succeeding pregnancy a further enlargement takes place. In the anterior lobe "the acidophil cells no longer dominate the field", but are crowded away from the sinuses, which they once lined, by neutrophilic cells derived from the normal chromophobes. "It is many months after parturition before the acidophils regain their former predominance" (Erdheim and Stumme[35]).

Though these changes are very different from those seen in acromegaly, there is some clinical evidence to support the suggestion that the short-lived pituitary hyperplasias of pregnancy may precede the onset of acromegaly. The sequence occurred in two of Cushing's cases (Cases II and XXIV), and the acromegalic signs

were followed by those of hypopituitarism. Moreover, the association with pregnancy is very clear in Marek's case in which transitory acromegaly developed during gestation in a 27-year-old primipara. The nose and jaws became larger and the teeth spread apart, the tongue increased in circumference, the tonsils swelled, and glycosuria, lassitude, and insomnia were present. All the signs disappeared during the puerperium (Falta[36]).

The relationship of pregnancy to pituitary conditions is further elaborated in the following quotation from *The Diseases of the Pituitary Body* (p. 235): "repeated involutions from the chromophobe hyperplasias of the Erdheim and Stumme type

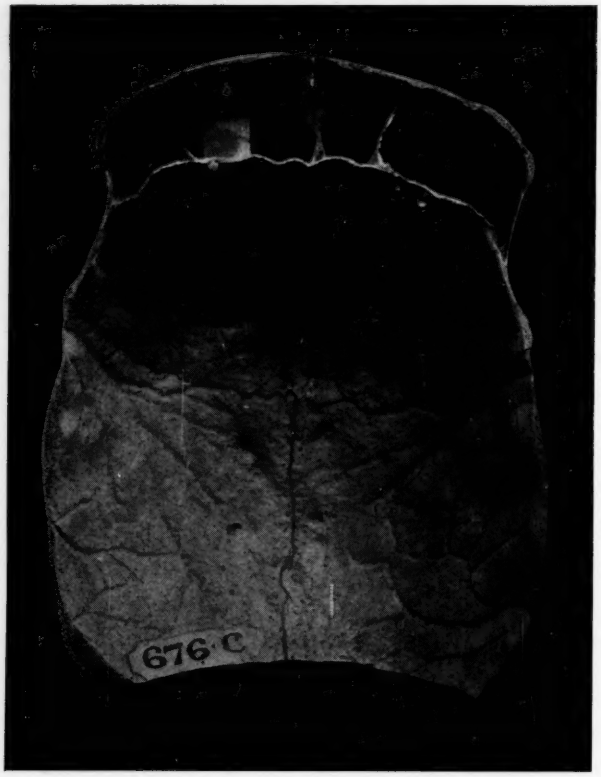


FIG. 79.—Anterior portion of an acromegalic calvarium, showing great enlargement of the frontal sinuses and thinning of the vault. From a woman, aged 40, who died in an asylum and who had shown marked signs of acromegaly for seventeen years. The body was very obese and the skeleton enormous. The thyroid was hypertrophied, and the kidneys and spleen greatly enlarged. The pituitary body was converted into a large cystic tumour, and had produced a cavity in the sella turcica as large as a small hen's egg. Death occurred from hæmatemesis, which was due to capillary congestion of the stomach's mucous membrane. (Dr. C. F. Beadles' case, *Edin. Med. Jour.*, 1898, 501.) (*R.C.S. Museum, No.* 3868.1.)

may bring about a physiologically inactive condition of the gland", bordering on the pathological, and so explain "a measure of hypopituitarism" and "account for the excessive adiposity, loss of hair, asthenia, subnormal temperature, and so on, not uncommonly seen in women after multiple pregnancies".

Puberty.—There is no question that the increase of growth that occurs in adolescence is definitely associated with puberty, and the fact that giantism develops in adolescence naturally suggests testicular influence. The increased lustfulness

of the early stages of acromegaly again emphasizes the linking up of the testicular and pituitary functions. Rapid growth in adolescence is probably due to physiological pituitary hypersecretion, and the glycosuria met with at that period, and in pregnancy, may be similarly explained. In all individuals at such times carbohydrate toleration is probably low (Cushing). (*See* pp. 79, 80.)

Infection.—There is both experimental and microscopical evidence that the pituitary body is affected by bacterial intoxication. Clinically, the various infections that have preceded the onset of acromegaly are tubercle, obscure pulmonary trouble, typhoid, scarlet fever, and rheumatism. In Rodriguez's[37] case of a girl, aged 16 years, an acromegalic giantess, extraordinary growth began between the fourth and fifth years, and she had suffered from meningitis at the age of three. (*See also* Henrot's case, p. 70.)

Another interesting fact may be noted: that when pituitary manifestations arise after infection or traumatism, it is acromegaly that follows infection, and hypopituitary symptoms that follow trauma.

Heredity.—The occasional occurrence of giantism or acromegaly in a family in which there is a definite tendency to skeletal overgrowth in more generations than one suggests that sometimes there exists a familial proclivity to functional instability of the pituitary. Transition from a physiological disturbance to a pathological state would be more likely to take place in the presence of such a predisposition than when the pituitary is endowed with the normal power of resistance. In the former case the onset of acromegaly might be determined by puberty, one of the infections, or a pregnancy.

TREATMENT

The treatment of acromegaly will be considered under the headings of: (1) Irradiation; (2) Surgical interference; (3) Glandular therapy.

1. **Irradiation.**—The use of X rays and of radium are included under this term. Its object is to promote atrophy of the anterior lobe cells and shrinkage of the gland, or, short of that, a diminution of the functional activity of the cells.

The different kinds of cells vary in their sensitiveness to irradiation. The eosinophil (acidophil) adenomata are said to be "very radio-sensitive, and to respond to X-ray treatment almost immediately", but "the chromophobe adenomata are radio-resistant, and while the increase of intracranial pressure can be reduced in these cases, the growth of the tumour cannot be influenced" (Kerley[38]).

The X rays and radium have each their appropriate place in treatment. The former can be used in the early stages of the disease by radiation from the surface, but the latter is unsuitable for surface radiation when the pituitary has to be attacked (Sargent and Cade[39]). It must be applied *in situ* in the form to be described below.

One of the earliest cases in which X rays were used was Beclerc's.[40] A young giantess, aged 16, was completely relieved in two months of severe headache, and the left field of vision was tripled after ten weeks' weekly radiation from the fronto-temporal region.

Similar cases have been recorded by J. H. D. Webster,[41] Teel,[29] and others. In these cases the X rays constituted the initial treatment, but they have also been used with advantage after operation. Frazier,[42] indeed, has employed both X rays and radium as a routine post-operative measure from 1917. In post-operative

treatment the rays are more effective if they are applied over the aperture in the skull. Radiation by the rays is indicated not only in the hyperpituitary stage of acromegaly, but also when the hypopituitary syndrome is present, if it is thought that the tumour growth is causing pressure atrophy of the acidophil cells and so leading to deficient secretion.

When radium is used it is applied locally after the tumour has been exposed by operation. The important structures in the immediate vicinity of the pituitary body are easily damaged, so the emanation from the element is preferred to pure radium. The emanation—known as 'radon'—is contained in small platinum tubes called 'seeds'; its energy is at its maximum when it is first given off, and steadily diminishes till none is left. The seeds, therefore, may be left *in situ* permanently. On the other hand, 'needles' contain small quantities of the actual element (radium dust), whose energy is perpetual—consequently needles must be removed. In situations in the brain other than the pituitary they may be preferred to 'seeds'. Two or three seeds are sufficient for insertion in a pituitary tumour, and as they have a tendency to fall to the bottom of the fossa they should be planted with care. Further, the possibility of excessive dosage "producing permanent blindness" must be kept in mind (Sargent and Cade[39]). Wakeley[43] has inserted nine radon seeds round about a pituitary tumour in a case of acromegaly in a woman aged 21. The patient was said to be "perfectly well" five weeks later.

2. **Surgical Interference.**—Operative treatment may be necessary, sometimes urgently so, to prevent threatened blindness or to relieve intense headaches. The intracranial symptoms are likely to be relieved, but the general signs are less influenced, though they may be improved. An operation is indicated when a patient who presents Marie's syndrome, with increased sellar measurements, develops an increasing hemianopsia. In most cases the proceeding adopted is the exposure of the anterior lobe or tumour by one of the several methods of approach, and the removal by curetting of a considerable proportion of the adenomatous or hypertrophied gland, or the evacuation of a cyst. Instead of partial removal, radon seeds may be inserted in suitable cases. The improvement that follows is often striking; headache vanishes, vision and the visual fields improve, and the patient may be so much benefited as to be able to resume his occupation. But this is not always the case, and blindness may be only postponed. In some cases a bitemporal decompression may be thought the wiser course.

After many procedures have been proposed, and some carried out, three routes for reaching and exposing the pituitary have gradually become defined: (1) An extracranial or nasal route, known as the 'trans-sphenoidal'; and (2) Two intracranial routes—(*a*) the 'frontal', and (*b*) the 'subtemporal'.

Frazier has laid down the following indications for deciding the choice (loc. cit., p. 223):—

1. A simple decompression—subsellar (trans-sphenoidal route)—with incision of the capsule, is indicated: (*a*) When there is no striking evidence of intracranial extension ("Usually atrophy of the clinoid processes implies a rupture of the diaphragm, and an intracranial extension"); (*b*) "When there has not yet been a spontaneous decompression which results from erosion of the sellar floor."

2. The suprasellar or intracranial route is to be chosen: (*a*) When spontaneous decompression has already taken place; and (*b*) When there is positive evidence of intracranial extension.

He considers that the suprasellar operation is a much more formidable procedure than the extracranial, because it implies an attempt at a more or less radical extirpation of the lesion—a criticism that does not apply to the insertion of radon seeds—whilst " after the relief of pressure by a subsellar decompression the growth of the lesion may be arrested by the use of radium and X rays ".

Trans-sphenoidal Operation.—The following is a brief description of the trans-sphenoidal operation as described by Cushing.[44] " The upper lip is drawn up and the transverse incision first advocated by Halstead for hypophysial operations is then made across the labial frænum. The incision is carried down to the anterior nasal spine of the superior maxilla." The operation then resolves itself into a submucous one, with removal of most of the vomer, the lower edge of the median plate of the ethmoid, and a small strip of cartilage. The prow of the vomer underlying the sphenoidal cells is identified and possibly removed. The sphenoidal cells are easily recognized, and the anterior and lower walls chipped away with long-handled nasal rongeurs, the lining membrane removed, and the sellar protrusion exposed.

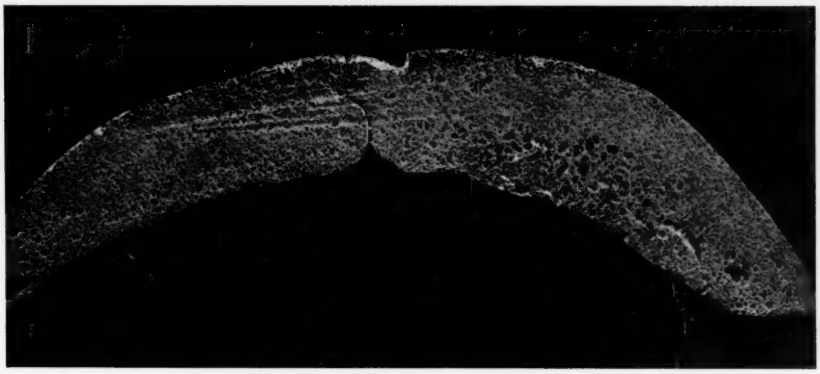


FIG. 80.—Transverse section through the parietal bones of an acromegalic skull resembling the cranium in osteitis deformans (Niccolucci). Natural size. (*R.C.S. Museum, No.* 3861.1.)

The bone is easily chipped away, and the dural covering or capsule is opened with a knife hook, and a crossed incision made. Such a degree of extirpation as is considered advisable is then carried out. A head-lamp, special retractors, and speculum are necessary, and all oozing must be stopped as the operation proceeds, so that every step can be seen. Drainage, which was used at first, is now omitted, and the incision under the lip closed with two or three catgut sutures.

" The procedure is median from the outset; it is conducted in favourable cases without entering the mucous-lined nasal cavity; it can be carried out in one session, and is somewhat less mutilating " than some similar methods, as the turbinates are merely flattened temporarily, and not removed.

Any surgeon contemplating the performance of this operation for the first time should read Cushing's description, in which valuable hints are given as to the avoidance of the various difficulties likely to be met with.

The chief value of the trans-sphenoidal method lies in the subsellar decompression. The necessary limitation and uncertainty of the extirpation that can be carried out by it add to the difficulty and the risks of the operation; and Frazier,[45] writing in 1928, states that notwithstanding the lower operative risk, it has been

abandoned in the Pennsylvania Clinic because recurrence of symptoms was not infrequent, and they had felt obliged to "adopt the transfrontal method as the procedure of choice."

Satisfactory results, however, may follow it, as a case reported by W. E. Saner[46], seventeen years after its performance, proves. The patient's vision was definitely improved and his strength recovered, and he had worked on a farm ever since. His appearance was strikingly acromegalic, but the circumference of his hands had diminished 1 in. and the size of his boots from No. 11 to 10.

Frontal Operation.—The frontal route is the simpler of the intracranial or suprasellar operations. It consists in an "incision from ear to ear across the vertex, and the scalp is pushed forwards over the supra-orbital ridges" (Wakeley). A large bone-flap is cut from the right frontal region, the dura mater is stripped from the orbital plates of the frontal bone, and then incised just in front of the small wing of the sphenoid. The frontal lobe is raised, and the optic nerves and chiasma, and the situation of the tumour, when it occupies the chiasmal region, exposed. The tumour is attacked above the chiasma and straight sinus. The operation is conducted from the right side, so that the left and more important frontal lobe is least disturbed.

Subtemporal Operation.—In the subtemporal operation the approach is made along the middle fossa. After the osteoplastic flap has been turned down the dura is opened and the temporo-sphenoidal lobe raised. There are important vessels, sinuses, and nerves to be avoided, but it may be preferable to the frontal route when the tumour occupies the interpeduncular region (Cushing). This was the method employed by Horsley.

3. **Glandular Therapy.**—The position of glandular therapy is not very assured, and so long as the true explanation of the hypopituitary syndrome is uncertain it must be regarded, to some extent, as an empirical method of treatment. Its results are not nearly so impressive as those obtained by thyroid feeding in myxœdema, or by the administration of insulin in diabetes. Frazier[47] had only three cases in his entire tumour series in which demonstrable improvement followed the ingestion of pituitary and thyroid extracts, but in all three the improvement was striking.*

Some judgement is necessary in the employment of the pituitary extracts. In the active state of acromegaly they would be likely to aggravate the symptoms, but when the pituitary secretion is failing and is deficient they may be used with some hope of improvement. In the latter case the whole gland extract should be given, because, when the pituitary is subjected to pressure, both lobes tend to be put out of action.

By such treatment, even though it makes but little impression upon the adiposity, the other pituitary symptoms may be distinctly benefited. "The body temperature is apt to regain its normal level, the blood-pressure becomes higher, constipation is less troublesome, and there is less drowsiness and often marked improvement in mental activity" (Cushing).

As an example of the kind of improvement that may be hoped for, the following case of Frazier's, in which a pituitary adenoma had been partially removed for

---

* Frazier looks upon thyroid extract as an effective supplementary agent, as experimentally the interrelationship between the thyroid and pituitary has been conclusively proved.

headache and blindness, may be quoted: The patient presented many of the stigmata of pituitary dysfunction, including adiposity, no facial or axillary hair, pubic hair of the feminine type, and mental apathy. (No mention is made of any acromegalic signs*.) A year later headache was not so severe, but he was otherwise unimproved; cerebration was slower, and he slept most of the time. On Jan. 1, 1927, pituitary feeding of anterior and posterior lobes was begun (2 gr. night and morning). On Feb. 20 the patient, from a somnolent, almost comatose state, had become alert and able to get out of bed into a wheel chair. On Aug. 25 he could get about unaided, somnolence had completely disappeared, and, six weeks before,

FIG. 81.—Transverse section of portion of the shaft of a phalanx from the same case as *Fig.* 74 showing a calcified projection into the periosteum (Ironside Bruce's node). Ossification has not advanced into the calcified mass from the cortical bone. (× 40.)

he had had his first nocturnal emission. At this time he was taking 1 gr. each of anterior and posterior lobe and of thyroid extract twice a day.

A corollary to pituitary feeding would be *grafting* if that procedure were not too impracticable in the human subject to demand serious consideration. Cushing,[48] however, was once able to take advantage of opportunity, and records an instance in which the implantation of the hypophysis of a new-born child maintained an improvement of deficiency symptoms when it became impossible to continue injections of the whole gland, which had been giving considerable relief. The implantation was made in the subcortex of the temporal lobe at the site of the original decompression.

---

* The reader is reminded that acromegaly is only one of several conditions associated with the pituitary body that may present the clinical features of the 'hypopituitary' syndrome. Probably the explanation of the symptoms is the same in all.

Most of the work upon glandular therapy is experimental, and the complexity of the physiological and pathological problems makes the subject rather bewildering.

In the preparation of this article much help has been given to me by many friends, and though in most instances it has been noted in the text, I desire here to express to them my grateful thanks, and especially to Sir Arthur Keith, the late Curator of the Royal College of Surgeons' Museum, Mr. T. W. P. Lawrence, Dr. Stebbing, Dr. Dean Lewis, of Johns Hopkins University, Professor Brash, of Birmingham, the Curator of St. Bartholomew's Hospital, and Dr. Frank Corner, whose interesting case is an important part of the groundwork of this paper. Nor must I omit to acknowledge the help derived from the MS. and complete bibliography which have been published in Mr. F. R. B. Atkinson's book on acromegaly. Three other friends, Dr. G. H. Rodman, Dr. C. F. Beadles, and Dr. Baly, to whom I have been indebted on this and many other occasions, passed away while I have been at work. Two of the illustrations in this paper are from Dr. Rodman's camera. Lastly, it is a pleasure once more to pay tribute to Messrs. George and Smith, and Miss Glasscock, of the College of Surgeons' Staff, to whose willing assistance the illustrations bear ample witness.

REFERENCES

[1] MARIE, P., "Two Cases of Acromegaly. Singular Non-congenital Hypertrophy of the Upper and Lower Extremities and Head", *Rev. de Méd.*, 1886, vi, 297.
[2] New Sydenham Society's publications.
[3] MARK, L. P., *Lancet*, 1914, ii, 1412.
[4] Medical Society of Rheims, *see* R. S. Med. Tracts, cccxxx. Marie's paper, Obs. 7, p. 319. "Acromegaly" (P. Marie and Souza-Leite). New Sydenham Society, 1891.
[5] CUNNINGHAM, *Jour. Anat. and Physiol.*, 1879, xiii, 508.
[6] THOMSON, A., *Ibid.*, 1890, xxiv, 475.
[7] HADDON and BALLANCE, *Clin. Soc. Trans.*, 1885, xviii, 325, and 1888, xxi, 201.
[8] BROCA, *Arch. gén. de Méd.*, 1888, ii, 656.
[9] FURNIVALL, *Trans. Pathol. Soc. Lond.*, 1898, xlix, 224.
[10] ROLLESTON, H. D., *Ibid.*, 237.
[11] MARK, L. P., *Acromegaly—a Personal Experience*, 1912.
[12] MARIE, *Bull. Soc. méd. des Hôp.*, 1896, xiii, 413.
[13] FALTA, *Diseases of the Ductless Glands*, 276.
[14] KEITH, SIR A., *Lancet*, 1911, April 15, 993.
[15] BEADLES, *Edin. Med. Jour.*, 1898, 501.
[16] ERDHEIM, *Virchow's Arch.*, cclxxi, 288.
[17] ERDHEIM, *Die Lebensvorgänge im normalen Knorpel und seine Wucherung bei Akromegalie*, 145.
[18] MARIE and MARINESCO, *Arch. de Méd. Exp.*, 1891, iii, 543.
[19] HUNTER, *Trans. Pathol. Soc. Lond.*, 1898, xlix, 248.
[20] CUSHING and DAVIDOFF, *Pathological Findings in Four Autopsied Cases of Acromegaly*, Rockefeller Monograph No. 22, 1927, 95.
[21] *Text-book of Histology*, 1904.
[22] DOTT and BAILEY, *Brit. Jour. Surg.*, 1925, xiii, 319.
[23] BENDA, *Berl. klin. Woch.*, 1900, xxxvii, 1205.
[24] SCHAFER, *Endocrine Organs*, Part ii, 193.
[25] CUSHING, Lister Memorial Lecture, *Lancet*, 1930, ii, 121.
[26] LEWIS, DEAN, *Bull. Johns Hopkins Hosp.*, 1905, xvi, 162.
[27] BAILEY and CUSHING, *Amer. Jour. Pathol.*, 1928, iv, 545.
[28] ENGLE, *Amer. Jour. Physiol.*, 1929, lxxxviii, 104.
[29] TEEL, *Endocrinology*, 1929, xiii, 522.

[30] ZONDEK and ASCHHEIM, *Klin. Woch.*, 1928, 1404.
[31] *Guy's Hosp. Rep.*, 1924, lxxiv, 402 (C. P. Symonds and Eckhoff); *Rev. neurol.*, 1922, xxxviii, 622; *Comptes rend. Soc. de Biol.*, 1913, lxxv, 483; *Endocrinology*, 1920, iv, 507.
[32] *Arch. of Internal Med.*, 1921, xxviii, 773.
[33] *Amer. Jour. Anat.*, 1930, xlv, 206.
[34] ASHNER, *Arch. ges. Physiol.*, 1912, cxlvi, 1.
[35] ERDHEIM and STUMME, *Beitr. z. pathol. Anat. u. allg. Path.*, 1909, xlvi, 1.
[36] FALTA, *Ductless Glandular Diseases*, 252; *Zentralb. f. Gynäkol.*, 1911, xxxv, 1612.
[37] RODRIGUEZ, *Rev. neurol.*, 1922, xxxviii, 716.
[38] KERLEY, *Recent Advances in Radiology*, 306.
[39] SARGENT and CADE, *Brit. Jour. Surg.*, 1931, xviii, 503.
[40] BECLERC, *Arch. Ront. Rays*, 1909–10, xiv, 149.
[41] WEBSTER, J. H. D., *Arch. of Radiol. and Electrotherap.*, 1919–20, xxiv, 261.
[42] FRAZIER, *Arch. of Ophthalmol.*, 1921, l, 217.
[43] WAKELEY, *Proc. Roy. Soc. Med.* (Clin. Sect.), 1930, xxiv, 481.
[44] CUSHING, *Diseases of the Pituitary Body*, 297.
[45] FRAZIER, *Ann. of Surg.*, 1928, lxxxviii, 1.
[46] SANER, *Ann. Otol. Rhinol. and Laryngol.*, xxxix, 66.
[47] FRAZIER, *Arch. of Neurol. and Psychiat.*, 1930, xxiii, 673.
[48] CUSHING, *Diseases of the Pituitary Body*, 320.

PSEUDO-MYELOMATOUS CARCINOMATOSIS

By L. COSIN

PRINCE OF WALES'S GENERAL HOSPITAL, LONDON

MARTIN, Dechaume, and Ben-Rais have drawn attention to the combination of multiple carcinomatous metastases in bone with Weil and Clerc's syndrome of splenomegaly and an anæmia, often hyperchromic, which is characterized by the presence of many immature red and white cells; there is rarely any great leucocytosis.

They describe the case of a woman, aged 54, who was admitted for widespread bony pains two years after a right radical excision of the breast for carcinoma. She was found to have splenomegaly and a hyperchromic anæmia, and radiograms showed the presence of many areas of rarefaction of bone, especially marked in the vertebræ. There were 1,580,000 red cells per c.mm., 37 per cent of which were nucleated; hæmoglobin was 37 per cent, giving a colour index of 1·18. Of 11,000 white cells per c.mm., 48 per cent were neutrophils, 15 per cent myelocytes, 15 per cent lymphocytes, and 22 per cent mononuclears. Post-mortem examination showed widespread replacement of the marrow spaces by new growth, and secondary deposits in ovaries, liver, spleen, and mediastinal glands. The close parallel between this case and that to be described will become apparent.

CASE REPORT

HISTORY.—Sidney C., aged 25, was admitted to hospital on Nov. 11, 1933, for pain and bruises, especially in the lower limbs, and great fatigue. There had been tenderness on pressure over the middle third of the sternum for the previous four months, and crops of petechiæ and bruises for the previous three months. Two months before admission the patient noticed severe throbbing pain in both lower limbs; this persisted for the next three weeks, and then moved to the shoulders, the right more than the left. As far as he knew he was apyrexial during this period. Much relief followed one week's rest in bed, but the symptoms rapidly became more marked on walking. He consulted his doctor, who was impressed by the pallor, enlarged spleen, and petechiæ. More recent symptoms were hæmorrhages from the gums and nose. The platelet count was later found to be 60,000 per c.mm. (Nov. 28). Winter cough and similar vague muscular pains, most marked in limbs, fingers, and shoulders, had been noticed for the previous four years.

ON ADMISSION.—The skin was of an earthy tinge, mucous membranes were pale, and there was little subcutaneous fat. There were a few petechiæ, most marked on the lower limbs, and a large superficial bruise was situated over a bony irregularity of the lower third of the right fibula. (There was no history of injury to this region.) The breath was fœtid, and the gums were soft and oozed blood. A few palpable lymph-glands in the right groin were not considered abnormal, but after the patient had been in hospital for eight weeks groups of mobile elastic glands suddenly appeared in both axillæ, groins, epitrochlear regions, and on both sides of the neck. The spleen was hard and uniformly enlarged down to the umbilicus. At no period of observation was the liver palpable. There was a soft apical systolic murmur, but the heart was otherwise normal, as were the respiratory and nervous systems. The optic discs were normal on admission, but, following a complaint of sudden mistiness of vision six weeks later, bilateral subhyaloid hæmorrhages were found, that on the right partially obscuring the macula. Normal gravitation occurred by the next day, leaving

the typical crescentic appearance, and vision improved simultaneously. Repeated urinary examination—especially for Bence-Jones proteose—revealed no abnormality. The skull and long bones were tender on palpation, and radiograms showed numerous circular punched-out areas of absorption of bone, all of approximately the same size and with very well defined edges (*Fig.* 82). This change was most marked in the skull, but could be seen in vertebræ, ribs, sternum, sacrum, ilia, and the bones of the limbs.

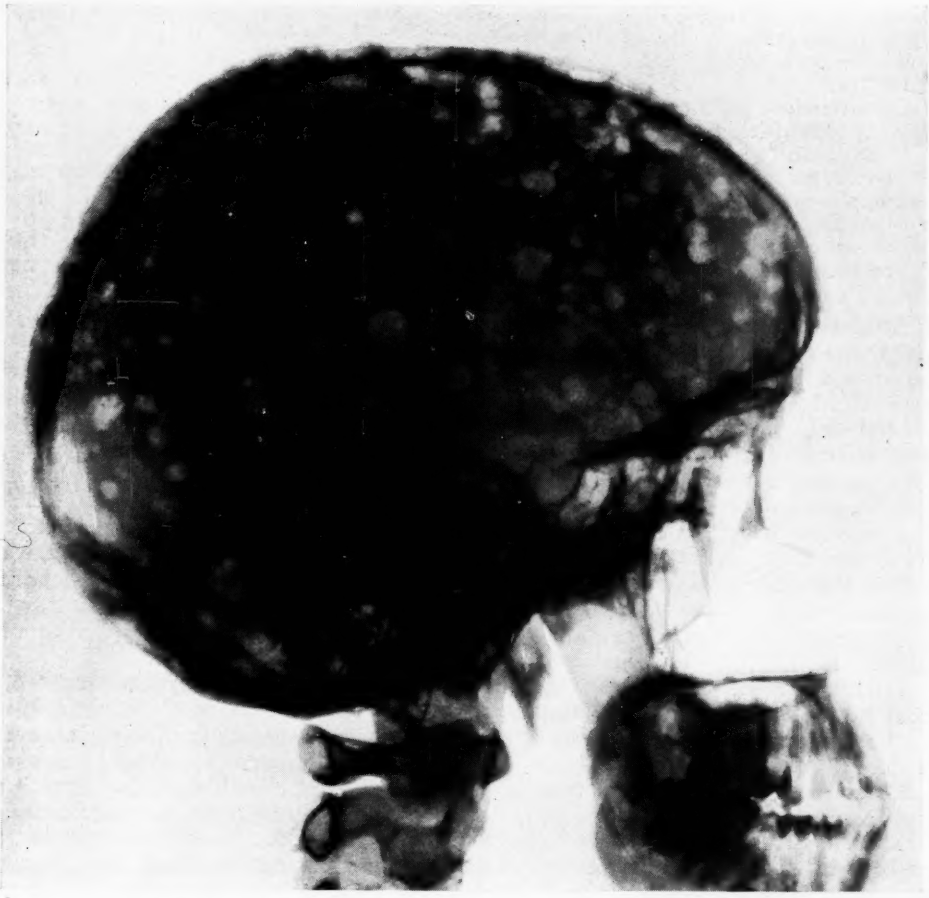


FIG. 82.—Radiogram of skull showing multiple areas of erosion of bone, each circular with clear punched-out edges, some perforating only the inner or outer table, and others extending through the calvarium.

Investigation showed that the plasma phosphorus, serum calcium, and serum phosphatase were normal. The Wassermann reaction was negative in the blood, and the blood-urea, uric acid, and cholesterol were also normal. The blood-sedimentation rate, however, was 120 mm. per hour. On admission there was a mild anæmia (hæmoglobin 60 per cent, red cells 3,000,000 per c.mm., colour index 1); the reticulocytes were increased (8·6 per cent); and there were 15 per cent myelocytes with a rapidly rising white-cell count (*see Table*).

Upon this evidence a provisional diagnosis of myelogenous leukæmia was made and deep X-ray therapy applied over the spleen (Nov. 21). A severe reaction followed, during which the muscular pains became very much more severe, and were associated with headache, vomiting, and rigors. The pulse-rate rose to 120 per minute and the temperature to 104°. The phagocytic index showed that there were only 4000 actively functioning neutrophils per cmm. Deep X-ray therapy was, therefore, discontinued. The hæmoglobin fell rapidly

despite massive doses of iron and liver. There were repeated hæmorrhages from nose, gums, and bowel, rarely profuse and easily controlled.

A peculiar symptom was polyuria during the last few days of life, when the average daily output was above 100 oz. The patient died on Jan. 21, 1934, after ten weeks in hospital. During this period there had been persistent pyrexia ranging between 99°. and 101°.

RESULTS OF BLOOD EXAMINATION AT VARIOUS STAGES OF THE DISEASE

	1933 Oct. 25	1933 Nov. 12	1933 Nov. 28	1933 Dec. 5	1933 Dec. 11	1933 Dec. 31	1934 Jan. 1
Red cells (millions) ..	3·6	3·0	2·8	2·4	1·8	1·6	0·75
Hb (per cent)	65	60	48	38	34	23	10
Colour index	0·9	1·0	0·85	0·8	0·9	0·7	0·7
White cells (thousands) ..	10·6	20	5	3·6	3·0	3·5	2·3
Neutrophils (per cent) ..	40·5	45	45	40	42	41	16
Myelocytes (per cent) ..	17	15	18	7	3·5	4	6
Lymphocytes (per cent) ..	30·5	23	17	34	37	50	78
Mononuclears (per cent) ..	5·5	13	19	14	16	2	0
Basophils (per cent)	1	1	1	3	1	3	0
Eosinophils (per cent) ..	3·5	3	1	2	1	0	0

AUTOPSY.—Post-mortem examination was performed by Professor Nicholson, and revealed multiple subcortical hæmorrhages in the brain, particularly in the region of the optic chiasma. There was a hæmorrhage anterior to the left caudate nucleus and also into the right lateral ventricle. Many pinkish-yellow nodules in the meninges had produced regularly punched-out areas in the inner table of the skull. In several places these had extended through to the outer table so that there was continuity between the dura and the overlying aponeurosis of the epicranius muscle. Similar areas had partially eroded the outer table only, while erosive deposits were found in the spongiosa and cortex of every bone examined, the change being particularly marked in the proximal long bones. Several firm white raised nodules were found on the pleura, while there was marked peribronchial thickening in the lungs, which were slightly œdematous and emphysematous. There were several subpericardial hæmorrhages and white deposits in the myocardium. No deposits were visible in the liver, which gave a positive Perl's reaction. The spleen was much enlarged and studded with white nodules. Both kidneys had similar deposits and subcapsular hæmorrhages.

HISTOLOGY.—Histological examination of the tissues was made by Dr. Simpson, to whom I am indebted for the following report:—

"The masses of growth present in the peribronchial tissues, under the pleura, and in the spleen, kidneys, myocardium, brain, and bones consist of large 'oat-celled' forms of an ill-differentiated carcinoma of the form now recognized as of bronchial origin. A tendency to differentiate in an 'acinar' manner, a feature to which attention was drawn first by Turnbull, occurs in the masses lying in the lung tissues, but not in the more distant metastases. The latter are isomorphic with the oat-celled growth seen first and are clearly more primitive and rapidly growing, presenting frequent necroses, some with hæmorrhage. In the parts taken from the lungs no definite site of origin is suggested, as is, unfortunately, so often the case, but there can be no doubt as to the actual nature of the growth. The deposits in bone require special attention. These are multiple centred and histologically of great activity of growth, the bony lamellæ showing active resorptive processes without much osteoclast cell reaction. No myeloid reaction is present. The impression of a most fulminating metastasis is given, the marrow tissues being displaced with great rapidity, and showing evidence of but the slightest resistance. No unusual features accompany the infiltrations in the spleen or other organs. Those in the spleen are scattered and of varying size, being placed in the reticulum, massively in the sinusoids, and scantily in the outer ring of reticular cells around the Malpighian bodies."

COMMENT

The reactions of bone to secondary metastases can be subdivided into two main types depending upon the degree of malignancy of the primary tumour. Should this feature be relatively low, there will be a correspondingly slow rate of

growth, so that the surrounding tissues are sufficiently irritated to enable them to react. This 'osteoplastic' type is best exemplified in carcinoma of the prostate, where the diffuse reactive condensation of bone may result in obliteration of the marrow cavity. When the malignant deposits are subperiosteal, in which event they are grouped round the large issuing venous sinuses (von Recklinghausen), there will be a 'malignant periostitis', with the laying down of much new bone. When malignant disease of the kidney, breast, thyroid, or lung affects the skeleton, it is more often of a higher grade of malignancy. Growth is more rapid and the bone is destroyed so that the 'osteoclastic' or rarefying reaction is seen. It is in this type that spontaneous fracture and collapse of vertebræ occur.

In both types, however, should a sufficient amount of bone-marrow be destroyed, the mechanical replacement of hæmatopoietic tissue will result in a progressive anæmia with the presence of many immature red and white cells. It might be expected that some degree of thrombocytopenia would occur and that petechiæ and hæmorrhages might be noticed, as was found in some of Weil and Clerc's cases. This was not commented upon in the case of Martin, Dechaume, and Ben-Rais, nor was it found in a case of C. F. Cosin's in which a woman of 33, with diffuse osseous carcinomatosis, hypochromic anæmia, and splenomegaly, was found at autopsy to have primary carcinoma of the ovary with multiple splenic metastases.

It would appear, then, that the well-known immunity of the spleen to carcinomatous infiltration is not maintained when a growth proves capable of infiltrating myeloid tissue. In all these three cases bony metastases were associated with invasion of the spleen by growth.

The enlargement of the spleen (more rarely of the liver) may be due to the metastases in these organs or to a myeloid metaplasia, as was seen in the case of Martin, Dechaume, and Ben-Rais.

In the osteoclastic type, when there is no evidence of an obvious primary source, disorders of calcium metabolism, such as hyperparathyroidism, must be considered. These can be excluded by investigation of the calcium balance. Osteitis deformans rarely gives rise to difficulty in diagnosis. The most difficult differential diagnosis lies between multiple myelomatosis and carcinomatosis. The blood picture in multiple myelomatosis is so variable as to be useless in diagnosis. It has been variously described as being normal, showing a mild hypochromic anæmia, or frankly leukæmic in type, especially in the later stages of the disease. It is usuallys tated that the enlargements of the spleen and liver do not occur in multiple myelomatosis, although deposits may occur there before they are found in the bones, but it must be obvious that providing there is sufficient mechanical replacement of bone-marrow the typical picture of Weil-Clerc's syndrome will appear, whatever the cause.

Bence-Jones proteosuria occurs in only 65 per cent of cases of multiple myelomatosis (Copeland), but it also occurs in some cases of carcinomatosis. Thus the absence of this substance cannot exclude multiple myelomatosis, nor can its presence confirm. In fact Bence-Jones proteosuria is of less value in diagnosis than is Weil-Clerc's syndrome. Biopsy is an unjustifiable procedure when merely used to satisfy idle curiosity, nor is it entirely without risk.

Radiography has been previously claimed to be the only test which will clearly differentiate the two conditions (Sutherland, Decker, and Cilley), for it is said that it is only in multiple myelomatosis that the perfectly circular, clear-cut

punched-out areas of rarefaction occur. The fallacy of this assumption has been proved in this case. Enlargement of the lymph-glands does not occur in multiple myelomatosis; it does not occur as commonly as might be expected in carcinomatosis, although Copeland reports a case of carcinoma of the stomach in which the first symptom was a widespread enlargement of the lymphatic glands with a blood picture typical of Weil-Clerc's syndrome. In the present case this lymphatic enlargement appeared after the patient had been in hospital two months, and only two weeks before death. It should be realized that the only evidence of carcinomatosis may be Weil-Clerc's syndrome with no radiographical bony changes whatsoever.

SUMMARY

A case of pseudo-myelomatous carcinomatosis occurring in a man, aged 25, is described. This showed radiograms typical of multiple myelomatosis and the presence of Weil-Clerc's syndrome of splenomegaly and anæmia, often hyperchromic, with many nucleated red cells and myelocytes. The total white count was rarely above normal. The importance of this syndrome in the diagnosis of carcinomatosis is stressed.

Other peculiar features of the case were the terminal polyuria, which might have been due to invasion of the pituitary or hypothalamic region, the difficulty of diagnosis even at autopsy, and the occurrence of splenic metastases. The frequent impossibility of differentiating between multiple myelomatosis and carcinomatosis without biopsy is pointed out. In both this case and that of Martin, Dechaume, and Ben-Rais, a high mononuclear cell-count was present.

My thanks are due to Dr. Douthwaite, Dr. Hurst, and Dr. Witts for permission to publish this case and for much helpful criticism and advice.

BIBLIOGRAPHY

COPELAND, M. M., *Arch. of Surg.*, 1931, xxiii, 23, 581.
COSIN, C. F., Personal communication.
GROVE, J. S., and KRAMER, S. E., *Amer. Jour. Med. Sci.*, 1926, clxxi, 250.
INGRAHAM, R., *Surg. Clin. N. Amer.*, 1927, vii, 877.
MARTIN, J. F., DECHAUME, J., and BEN-RAIS, H., *Bull. de l'Assoc. pour l'Etude du Cancer*, 1927, xvi, 612.
RAGENEAU, *Thèse de Lyon*, 1926, quoted by Martin.
SUTHERLAND, C. G., DECKER, F. H., and CILLEY, E. I. L., *Amer. Jour. Cancer*, 1932, xvi. 1457.
THOMAS, H. B., HIRSCH, E. F., and BLAINE, E. S., *Jour. Amer. Med. Assoc.*, 1928, xc, 89.
VON RECKLINGHAUSEN, quoted by Copeland.
WEIL, P. E., and CLERC, A., *Semaine méd.*, xlvi, 373.

OMENTAL TORSION WITH UNUSUAL SYMPTOMS

By C. R. SALSBURY, Kingston, Ontario

Omental torsion is not so rare as was previously considered, and reports of cases are becoming increasingly common. The time may be already reached when publication of cases for statistical purposes only is no longer justified. The following cases are recorded, however, because in one the diagnostic problem was one that has not, so far as could be discovered, been previously reported.

Case 1.—A male, aged 57, was admitted to the Salford Royal Hospital because of abdominal pain. This was felt first in the epigastrium, but shifted to the right iliac fossa in approximately twelve hours. He had vomited twice in the twenty-four hours since the onset, but there had been no bowel movement. Examination revealed the scar of an operation for inguinal hernia on each side, tenderness in the right iliac fossa, a dry tongue, temperature 98·2°, pulse 84, and respirations 24.

A diagnosis of acute appendicitis was made and operation performed. The appendix was normal but was removed. The operation report states: "Torsion of greater omentum present; excised," but there is no description.

Case 2.—E. J., a well-developed boy of 9 years, was admitted to the Salford Royal Hospital, under Mr. E. D. McCrea, on Aug. 14, 1933. He complained of pain in the right side of the abdomen, beginning during the afternoon of Aug. 12. According to his story he had spent the afternoon at a football match, and a lady had leaned against him, with her elbow against his abdomen, during most of the game. He ascribed his pain to the pressure of her elbow. As he did not eat much that night, he was given a laxative. On the following day he ate a good breakfast went for a walk, ate again at noon, but refused the night meal. There was one bowel movement with no complaint of pain.

During the afternoon of Aug. 14, he again complained of pain, and lay with his thighs flexed. He was seen by his physician and sent to hospital. There had been frequent urination for the two days preceding his admission.

Fifteen months before this he had had fifteen teeth removed because of 'stomach trouble' of many months' duration. This had not troubled him since the extractions. He had had mumps at the age of 3, chicken-pox at 4, scarlet fever at 5, and whooping-cough. His mother, father, and only brother were in good health.

On Examination.—Examination, except of the abdomen, was of no importance. Temperature, pulse, and respiration were normal. The most prominent finding was a greatly distended bladder. Catheterization was performed and 20 oz. removed. Urinalysis revealed nothing abnormal. With the bladder empty, a large mass could be felt in the right side of the abdomen. It extended up to the liver and down to the anterior superior spine. (Note made at the time, "Probably an appendicular abscess, but very high.")

Aug. 15.—He required catheterization in the morning and evening. The mass was smaller in the morning, but definitely larger in the evening. Because of the position of the swelling and its variation in size, hydronephrosis was suspected and cystoscopy decided on. The white-cell count was 16,000. Differential not done.

Aug. 16.—Cystoscopy by Mr. McCrea. The bladder held 4 oz. without discomfort. There was a little débris, but the mucosa appeared normal. The left ureteric orifice was prominent, but the right was small and seen only with difficulty.

After the intravenous injection of indigo-carmine the dye appeared in seven minutes from the left ureter and flowed freely. None had appeared from the right side in fifteen minutes. A ureteric catheter was inserted into the right ureter and fluid came freely but without any trace of dye. The catheter was left in place. The urine from the right kidney showed red and white blood-cells, but not in sufficient number to be of any diagnostic significance.

Aug. 17.—" Abdominal mass varies in size, but has not disappeared."

Aug. 18.—The ureteric catheter was removed. There had been no further change in size.

Aug. 25.—Uroselectan was given intravenously. Both kidneys showed up well. There was slight enlargement of the right ureter and renal pelvis. The size of the swelling had not altered.

Operation was decided on. A note made before operation presents the following summary: " For hydronephrosis: normal temperature; dilatation of right ureter and pelvis; the sudden onset; location of the mass and its variations in size. Against hydronephrosis: failure to disappear after ureteral catheterization; the acute retention; the X-ray appearance which, although showing some dilatation, certainly was not that of a hydronephrosis of sufficient size to produce the abdominal swelling."

Operation (Aug. 30, Mr. McCrea).—A low oblique incision was made just medial to the right anterior superior spine, so that the kidney, ureter, or abdominal cavity might be explored. As soon as the muscles were divided it became obvious that the mass was intraperitoneal, and the peritoneum was opened in the line of the incision. A very tense, shiny mass, about $3\frac{1}{2}$ in. in diameter, appeared in the wound. This occupied the right inferior part of the greater omentum, which was twisted into a rope of approximately 5 in., the end nearer the tumour being much more tightly twisted than the central end (*Fig.* 83). The direction of rotation was clockwise and there were two and a half turns. There were light adhesions to the anterior abdominal wall. These, obviously, must have occurred after torsion. Numerous enlarged lymph-glands were scattered throughout the mesentery of the small bowel and there were some in the omentum itself. They were neither caseous nor calcified. The twisted omentum was ligated in sections and cut through, and the abdomen was closed with a small drain to, but not through, the peritoneum. The wound healed by primary union.

The von Pirquet skin reaction was negative and no history of tuberculosis could be obtained for any member of the family.

On first getting out of bed the boy walked with the typical gait of flexion contracture of the right hip. This seemed to be due to a fear of extending the

thigh, as there was no limitation of passive movement and no paralysis. The limp gradually disappeared, and when discharged on Oct. 2 he was walking quite normally. He has been seen several times since and is perfectly well.

DISCUSSION

Acute omental torsion is by no means rare. At least 225 cases have been recorded: Morris[1] 217, Jeffries[2] 4, D'Errico[3] 2, and the present 2.

Case 1 presents nothing new, but illustrates two very common findings—that a previous operation for hernia is a very strong predisposing factor and that the usual pre-operative diagnosis is acute appendicitis.

FIG. 83.—*Case* 2. Torsion of the omentum.

Case 2 is of much greater interest. According to the classification of Morris, this is an acute unipolar torsion, complete and without hernia. Of the reported cases with sufficient data to classify, 22 per cent are of this type.

The pathological diagnosis, unfortunately, cannot be unequivocally stated. Microscopic examination showed a thick fibrous wall with no evidence of tubercle formation but without an endothelial lining. The contents were thick, homogeneous, practically colourless, with no caseation, necrosis, or hæmorrhage. The glandular enlargement suggests tuberculosis, but the negative skin reaction is

interesting. Taking all things into consideration, however, we feel that the condition was tuberculous. Is this the real explanation of his symptoms of fifteen months previously?

This seems to be the fifth youngest case on record, there being one of 3 years, two of 5, one of 7, and this one in a boy of 9. In young children omental torsion is much more likely to be due to cyst than is the case in an adult. A cyst was found in the child of 3 and in one of the 5-year-old cases. The specimen in this case was actually a cyst, whatever its etiology.

The case was admitted to hospital as a probable acute appendicitis. This is the most common diagnostic error, occurring in 60·02 per cent of all cases in which the pre-operative diagnosis was given. As already described, later developments suggested a hydronephrosis. We have failed to find a record of any other case with urinary symptoms.

The frequency of urination during the first few days and the slight dilatation of the right ureter and pelvis were probably due to the direct pressure of the tumour. Or was it retention overflow? The acute retention is much more difficult to explain.

The apparent variation in size of the palpable swelling was probably rather a variation in tension, the result of partial untwisting and retwisting. It is interesting to note that this occurred only during the first few days, giving us a reasonably reliable guide to the date of the formation of the adhesions to the anterior abdominal wall.

SUMMARY

Two cases of acute omental torsion are recorded. One case showed several interesting and unique features leading to difficulties of diagnosis, and we have attempted to explain these in terms of the lesion found.

I wish to thank Mr. E. D. McCrea for permission to report these cases, for his assistance in searching the literature, and for his many valuable suggestions during the preparation of the paper.

REFERENCES

[1] MORRIS, J. H., *Arch. of Surg.*, 1932, xxiv, 40.
[2] JEFFRIES, J. W., *Ann. of Surg.*, 1931, xciii, 761.
[3] D'ERRICO, *New Eng. Jour. Med.*, 1930, cciii, No. 24.

STRANGULATED INTERNAL HERNIA: REPORT OF CASES OF STRANGULATION IN THE FOSSA ILIACO-SUBFASCIALIS AND THROUGH THE FORAMEN OF WINSLOW

By G. F. LANGLEY

SENIOR RESIDENT OFFICER, THE GENERAL HOSPITAL, BRISTOL
LATE RESIDENT SURGICAL OFFICER, THE ROYAL INFIRMARY, BLACKBURN

Only three cases of hernia into the fossa iliaco-subfascialis of Biesiadecki are mentioned in the literature, and the records of these are indefinite. The following case of strangulation of ileum in this rare fossa appears worthy of record. The second case, strangulation of jejunum in the lesser sac of peritoneum, is less rare, but exemplifies the occurrence of double intestinal obstruction so accurately described by Finsterer.[1]

CASE REPORTS

Case 1.—**Strangulation of ileum in the fossa iliaco-subfascialis of Biesiadecki.**

History.—Mrs. Rachel H., aged 70, was admitted to the Blackburn Royal Infirmary on June 9, 1933. For four days she had complained of severe colicky abdominal pain in the umbilical region; vomiting had been almost continuous since the onset, and had been fæculent for over three days. For three days there had been absolute constipation, and three turpentine enemata had produced negative results.

For the past three months there had been fullness and discomfort in the umbilical region shortly after meals, which had sometimes been relieved by vomiting. The patient's bowels had been opened every second day after taking liquid paraffin, and neither blood nor mucus had been noticed in the stools. She had seven children and there was nothing of note in the gynæcological or urinary history. For many years she had suffered from severe chronic bronchitis and œdema of the feet.

On Admission.—The patient was gravely ill, the tongue was dry and furred, the skin was dehydrated and inelastic. Temperature 98°, pulse 106, respirations 36. Fæculent material was vomited twice during the examination. The abdomen showed central distension, the flanks were flat, and peristalsis was seen and heard across the umbilical region. A deeply placed, ill-defined mass was detected in the right iliac fossa, the percussion note was resonant, and there was marked tenderness and some muscular guarding in this region.

Diagnosis.—A pre-operative diagnosis was made of: (1) Gall-stone ileus; (2) Carcinoma around the ileocæcal valve; (3) Appendicitis causing lower ileal obstruction. It was decided to perform an emergency ileostomy under local anæsthesia.

First Operation (June 9).—After preliminary saline infusion the abdomen was opened through a small gridiron incision in the right iliac fossa under novocain anæsthesia. The ileum was greatly distended and the cæcum was empty; a tender fixed mass was felt below the cæcum in the iliac fossa, but the patient was *in extremis* and it was not explored further. A Witzel type of ileostomy was performed just proximal to this mass and a No. 12 catheter was inserted.

Post-operative Course.—This was satisfactory; free drainage occurred from the tube and the patient's condition improved rapidly. After thirty-six hours the tube was clamped intermittently and a turpentine enema following upon an injection of pituitrin produced the passage of flatus. On June 12 the tube was clamped most of the day and preparation was made for a barium X-ray examination on the following day to guide in further treatment.

On the evening of June 12 the patient had a recurrence of her previous symptoms; greenish fluid was vomited several times and no drainage could be obtained from the ileostomy tube even after gentle irrigation. I concluded that either the tube had become dislodged or

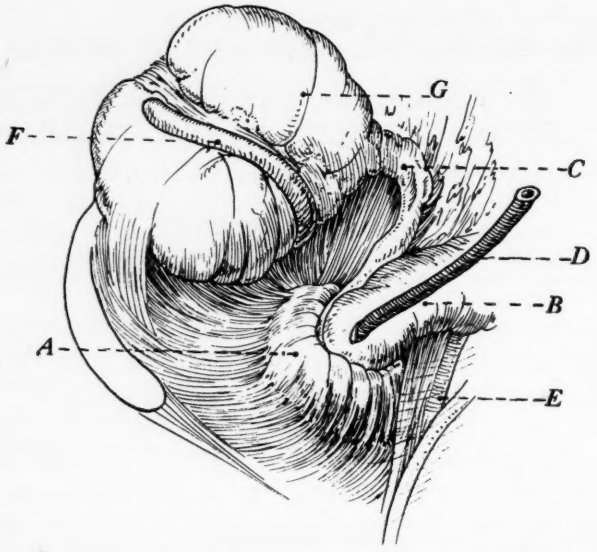


FIG. 84.—Sketch of hernia into fossa iliaco-subfascialis showing condition at operation. The cæcum and ileocæcal valve are retracted upwards to expose the iliac fossa and the hernia which is in the middle thereof. Shiny peritoneum covers all structures except the catheter. *A*, Hernia elevated above the iliac fossa, plum-coloured and covered by peritoneum; *B*, Dilated proximal ileum; *C*, Empty lower ileum; *D*, No. 12 rubber catheter entering proximal ileum at hernial orifice; *E*, External iliac vessels; *F*, Appendix lying free over cæcum; *G*, Under surface of cæcum (lifted up).

else it had caused a kinking with secondary obstruction, and, as the patient was in a rather better condition, decided to explore under spinal anæsthesia.

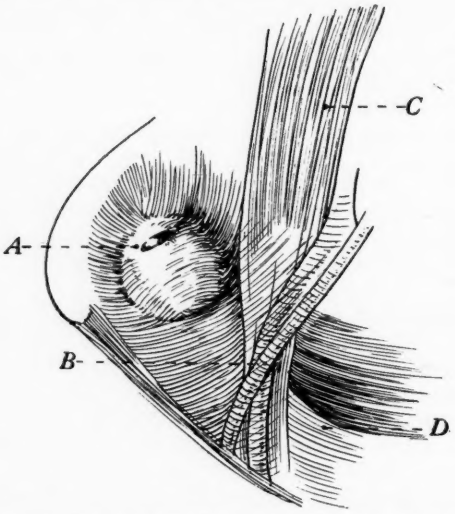


FIG. 85.—Diagrammatic representation of hernial sac in middle of right iliac fossa—bowel not shown.
A, Slit-like orifice of hernial sac; *B*, External iliac vessels; *C*, Psoas magnus muscle; *D*, Pelvic cavity.

SECOND OPERATION (June 12).—Through a right paramedian incision the ileum and jejunum were seen to be distended, but the cæcum and lowest 4 in. of ileum were collapsed. The ileostomy tube was in the lumen of the bowel, but its tip was fixed inside a plum-coloured

mass on the posterior wall of the iliac fossa into which the distended ileum and collapsed lower ileum were seen to enter. This mass, the size of a tangerine, was separated by 2 in. of parietal peritoneum from the peritoneal ligaments of the cæcum, but the fundus of the cæcum almost reached its upper portion; its outer edge was 1½ in. internal to the anterior superior iliac spine, while its inner edge reached nearly to the outer border of the psoas muscle.

The orifice of the hernia was on the upper internal aspect and the tip of the catheter was seen to be inside the distended proximal ileum entering the sac. The peritoneum over the sac was non-adherent and was incised, but the hernia was seen to have occurred deep to the iliac fascia of which a thick band across the neck of the sac had to be cut before the bowel was liberated. Four inches of ileum had been strangulated but were viable, a recent constriction groove was seen across the end of the catheter, and a roughened annular patch 1½ in. distal to this suggested the presence of an older constriction groove which might have been the cause of the earlier strangulation. The ileostomy commenced to drain well and the boundaries of the sac were investigated.

The neck of the sac consisted of a slit-like band of iliac fascia, and its anterior wall was formed of this structure. It was lined by parietal peritoneum through which, on the deep surface, the iliacus muscle fibres were seen. The outer border of the psoas muscle was palpable by the finger inserted into the sac. Two catgut sutures closed the sac, and the wound was sutured, leaving the ileostomy tube protruding from the original incision.

Post-operative Course.—The patient recovered well, and after clamping the catheter intermittently after the thirty-sixth hour it was removed on the eighth day. The wounds healed well, and the patient was discharged from hospital three weeks later.

Case 2.—**Double intestinal obstruction due to stenosis of colon with hernia of ileum through foramen of Winslow.**

HISTORY.—Thomas K., aged 70, was admitted to the Blackburn Royal Infirmary on Jan, 1, 1934. For six hours he had complained of intense colicky central abdominal pain and frequent vomiting; there had been no bowel action for two days, and no flatus had been passed for the preceding six hours.

A left inguinal hernia had been present for years, but had given rise to no trouble. Two years previously he had been admitted to another hospital suffering from "ulcer of the stomach", and after X-ray examination had been treated by diet and medicine for four weeks. He had not been improved by this treatment, and for the past two months had suffered from colicky umbilical pain and vomiting after food without relief of the pain. The bowels had become increasingly constipated for three months, and increasing doses of aperients had been necessary to obtain an action every third day. No blood or slime had been detected, and he had lost weight rapidly.

ON ADMISSION.—The patient was gravely shocked; temperature 95°, pulse 92. The skin and subcutaneous tissue was dehydrated, the vomitus was copious and of a dark coffee-ground nature. A vaginal hydrocele was found in the left side of the scrotum, but there was no hernia. The abdomen showed a very obvious distension above the umbilicus, reaching on the right side nearly to the costal margin and on the left to beneath the ribs. This region was very tender, there was some muscle-guarding, and the percussion note was resonant. There was a visible and palpable ballooning of the cæcum, and an ill-defined swelling in the region of the pelvic colon was noted. Rectal examination was negative.

DIAGNOSIS.—A pre-operative diagnosis was made of strangulated paraduodenal hernia with a probable concomitant colonic obstruction due to carcinoma of the pelvic colon. The epigastric swelling seemed to be the cause of the acute symptoms and might account for the previous 'gastric' history if it were a long-standing internal hernia; the history of increasing constipation and the ballooned cæcum suggested a more chronic colonic obstruction. It was therefore decided that this might be an example of double intestinal obstruction as described by Finsterer, and preparation was made for the performance of an ileostomy as in the previous case. While preparation was being made in the theatre for this to be done under local anæsthesia the patient vomited copiously and died.

AUTOPSY.—There was gross distension of the lesser sac of peritoneum, and the gastro-hepatic omentum was œdematous and infiltrated with blood. A loop of jejunum, 2½ ft. long, was found to have entered through the foramen of Winslow and was tightly strangulated in the lesser sac. The bowel appeared to be non-viable. The cæcum was ballooned with gas to about 7 in. in diameter and the ascending and transverse colon were distended. The whole

pelvic colon showed extensive intramural fibrosis, narrowing the lumen to the size of a quill. There were several inflamed diverticula and many pericolic adhesions, but no carcinoma was present. The fæces were hard and black owing to a bismuth mixture ordered by the patient's doctor, and there was obviously a colonic obstruction due to the fæcal impaction above the stenosed colon. There had thus been a definite double intestinal obstruction; the large internal hernia had probably been present for years causing mild symptoms, and the onset of strangulation had been accelerated by the development of a subacute obstruction of the colon causing increasing distension of the jejunum. There was no ulceration of the stomach or duodenum, and the gall-bladder was healthy.

THE PARACÆCAL HERNIÆ

Moynihan[2] collected and described all available records of paracæcal herniæ up to 1906, and, including these, I have been able to collect 42 cases from the literature. The site of the hernia has been as follows, using the classification of Moynihan and Rendle Short[3]:—

1. Hernia into the ileo-appendicular fossa	10
2. Hernia into the retrocolic fossa	23
3. Hernia into the fossa of Hartmann	2
4. Hernia into the fossa iliaco-subfascialis, including case of hernia of appendix described by Mott	3
5. Hernia into lateral cæcal fossa, described by Rendle Short ..	1
6. Hernia into anomalous openings	3

The anatomy of these fossæ has been described in great detail in Lord Moynihan's book and that of the last two types has been detailed in the various papers.

The Fossa of Biesiadecki (Iliaco-subfascialis).—This fossa is also called the subcæcal or iliac fossa or the fossa infracæcalis by various writers. It is situated in the middle of the iliac fossa and its size varies from a small transverse slit to a large fossa 2 in. in diameter with a wide elliptical mouth. The orifice is directed upwards and is bounded in front by a fold of iliac fascia running towards the iliac crest. Biesiadecki[4] demonstrated that the fascia in the upper half of the iliac fossa is lax and freely movable upon the iliacus muscle, whereas that in the lower half is more firmly bound down. Tarenetzky[5] showed that the junction of the two is often marked by a sharp upwardly concave fold, and further that this fossa can exist on either side of the abdomen.

I have dissected this region in a large series of autopsies and have been unable to demonstrate this fold of Tarenetzky in most, but when it has been present I have always found that the psoas parvus muscle has been exceptionally well developed. The psoas parvus is present in 45 per cent of people and is inserted into the fascia at the level of the ilio-pectineal eminence, from which strong bands of fibrous insertion radiate fan-wise towards the anterior superior iliac spine, Poupart's ligament, the posterior lamella of the femoral sheath, and also gain direct attachment to the ilio-pectineal eminence via the ilio-pectineal septum, which passes between the psoas and pectineal muscles. I have seen a well-marked fold of Tarenetzky in nine cases and on each occasion have noticed a very strong fascial insertion of the psoas parvus muscle, which has been the direct cause of the fold, passing towards the anterior superior iliac spine. I have demonstrated this point in a full-term fœtus in which bilateral folds were present associated with bilateral psoas parvus muscles, but in another fœtus in which there was a unilateral psoas parvus muscle the

fold was present only on the side of this muscle. The development of the fossa iliaco-subfascialis would therefore seem to be dependent upon the presence of a strong psoas parvus muscle whose fibrous insertion into the anterior superior iliac spine gives rise to the fold of Tarenetzky.

Hernia into the Fossa of Biesiadecki.—Moynihan quotes two cases. One is that of Engel, who found this hernia incidentally in a man who had died from pneumonia. Engel's description is: "The cæcal pouch was dilated so as to contain the small intestine with the exception of the upper portion of the ileum. The orifice of the sac admitted two fingers. As this sac was developed wholly in the right half of the abdomen the cæcum was pushed above and to the left of the umbilicus, and the colon and sigmoid flexure were pressed to the left. The intestine was distended with gas but could be removed from the sac quite easily and could be easily replaced." Moynihan, commenting on this description, says that it is "meagre and insufficient". Engel describes it as a case of retrocæcal hernia, but Moynihan agrees with Leichtenstern in regarding it as a case of hernia into the fossa iliaco-subfascialis.

The second case quoted by Moynihan is that of Mott, who showed the specimen to the London Pathological Society. "The vermiform appendix measured 7 in. It turned up behind the cæcum forming a sigmoid band, and terminated in a peculiar pouch 1½ in. long in the anterior part of the iliac fossa. This pouch has been described as the infra- or retro-cæcal fossa. Mr. Treves termed it the fossa iliaco-subfascialis. There was apparently a small artery running along the pouch."

The third case, not described in Lord Moynihan's work, was one of strangulation of ileum in this fossa and was operated on by Mr. Dunn at Guy's Hospital. It is referred to in Rowlands and Turner's *Operations of Surgery*,[6] but unfortunately no further details are available.

The case described here would therefore appear to be the only detailed record of a strangulated hernia into the fossa iliaco-subfascialis. The case of Engel appears to belong to the category of arrested rotation of the gut and to be rather of the nature of a congenital malposition as described by Edmund Andrews[7] than a genuine example of acquired hernia into this fossa.

SYMPTOMATOLOGY AND DIAGNOSIS

1. Cases with No Symptoms.—Many cases of internal hernia have been found at autopsy or during laparotomy for other lesions where there have been no symptoms referable to the hernia.

2. Cases with Chronic Abdominal Symptoms.—Several cases of paracæcal hernia have been found during operation for chronic appendicitis (Atherton[8]) and recurrent colic (Rock Carling and Jones,[9] Coley and Hoguet[10]). Both the patients described in this paper gave a history of gastro-intestinal symptoms which might have been due to distension of the bowel within the hernia without actual strangulation.

3. Cases of Strangulation.—Most cases have been discovered during operation for an acute abdominal lesion; the correct diagnosis is rarely made.

In the table on p. 124 my case is included as intestinal obstruction.

CASES PRESENTING ACUTE SYMPTOMS (27)

Diagnosis	Appendicitis	6
	Ovarian lesion	1
	External hernial strangulation	2
	Labour pains	1
	Intestinal obstruction	16
	Paracæcal hernia	1

A palpable mass has been noted in cases described by Riese,[11] and by Mansell Moullin,[12] and in my own. Coley and Hoguet, however, found a swelling in a chronic case of retrocolic hernia which they diagnosed.

Moynihan groups the symptomatology as follows: (1) Acute strangulation; (2) Recurrent subacute obstruction; (3) Palpable tumour formation—(*a*) The swelling is localized to a definite region, (*b*) Gurgling peristaltic sounds are often heard over the tumour, (*c*) The size and tension of the swelling are increased when strangulation occurs.

The obstruction in all cases is in the small gut, and pain is thus of a colicky nature and umbilical or epigastric in site, but, with the onset of local peritonitis in the hernial sac, there may be a shifting of the pain to the appendicular region. Shock is often less in internal hernial strangulation owing to the tightness of the orifice often being less than in external hernia, with less violent constriction of the mesentery.

The diagnosis of a strangulated internal hernia is thus only likely to be made by exclusion of obvious causes of small-gut obstruction, such as external herniæ, post-inflammatory adhesions, etc.; the presence of a high intestinal obstruction in association with a tender, resonant mass, probably with slight muscular guarding, occurring in one of the recognized sites for the retroperitoneal fossæ, should suggest the possibility of an internal hernia.

The results of 26 cases of paracæcal hernia with strangulation (including the present case) show that there is considerable delay in the commencement of treatment and a resulting high mortality-rate:—

RESULTS IN 26 CASES OF STRANGULATED PARACÆCAL HERNIA.*

Operated upon	20
Recoveries after operation	14
Deaths after operation	5
Deaths without operation	6
Uncertain result	1
Mortality after operation	18·5 per cent
Longest duration of symptoms	21 days
Shortest duration of symptoms	24 hours
Average duration of symptoms	5·4 days
Average duration of symptoms in fatal cases	5·1 days
Cases requiring resection	4
Deaths after resection	1
Recovery after resection	3

* These figures include only those of which I could obtain more or less detailed records.

Rendle Short[13] in 1925, reviewing the literature, found a mortality of 23·5 per cent in retrocolic herniæ and 20 per cent in the ileo-appendicular variety, the average being thus 21·7 per cent in these types.

DOUBLE INTESTINAL OBSTRUCTION

Finsterer collected 44 cases of double acute intestinal obstruction from the literature and reported a case of his own of simultaneous strangulation in a properitoneal inguinal hernia and in the retrocolic fossa. A brief summary of this case is appended :—

Finsterer's Case.—A male, aged 33, noticed an inguinal hernia for four months. He was admitted with four days' history of acute intestinal obstruction with signs of strangulation of this hernia. Spontaneous reduction of the hernia occurred with relief of symptoms. Twenty-four hours later there was a recurrence of symptoms and the hernia was again strangulated. Laparotomy through a right pararectal incision revealed a large properitoneal hernia near the right internal abdominal ring, with a diverticulum extending along the inguinal canal. After division of the sac 10 cm. of bowel were liberated, but the intestine was still anchored by its distal end. Further exploration showed the distal ileum to be strangulated in a retrocolic hernia. This portion was freed and 1·5 cm. were resected; continuity was established by end-to-side anastomosis with the cæcum. The patient recovered.

Finsterer classifies cases of double intestinal obstruction into two groups :—

1. Primary Chronic Intestinal Obstruction followed by a resultant hernial strangulation precipitated by the chronic intestinal distension (" Kombination Ileus " of von Hochenegg).

2. Double Acute Obstruction.—This includes double external hernial strangulation, external plus internal hernial strangulation, hernia plus volvulus, etc.

The mortality of these cases of double intestinal obstruction in 75 per cent owing to the overlooking of the second obstruction. The anal-ward obstruction is always primary, and, if situated in an external hernia, the higher lesion is likely to be missed; Finsterer therefore advises that in all cases the distal loop should be carefully examined as well as the proximal. If the distal loop is dilated, the inference that there is a lower obstruction is obvious, and this should be sought. The proximal loop should be drawn well down, if it appears to be tethered, and the cause of this should be investigated, as this tethering may be the only indication of a higher obstruction due to an internal hernia.

The case of internal hernia through the foramen of Winslow reported in this paper belongs to the first group of " Kombination Ileus." The danger would appear to be less than in Finsterer's second group, as the hernial strangulation is the more prominent feature, and, in external herniæ, the distension of the distal loop would be more obvious and would lead to investigation. A real danger would, however, arise in a case such as I have described if the operation of blind cæcostomy were contemplated in view of the gross cæcal distension. I have seen a case in a woman of 60 presenting similar features of acute intestinal obstruction with ballooning of the cæcum. A blind cæcostomy was performed under local anæsthesia but failed to relieve her pain or vomiting. At autopsy a carcinoma of the transverse colon was found to be causing obstruction, but the terminal event was an acute jejunal obstruction due to kinking by adhesion to the growth.

It appears, therefore, to be essential to be aware of the possibility of double intestinal obstruction in every case, and if circumstances have prevented thorough examination at the time of operation, any unexpected interruption in the immediate post-operative course should lead to a rapid investigation to

eliminate this factor. The necessity for adequate exposure and examination of both loops in all hernial strangulations, and for laparotomy rather than blind enterostomy in all suitable cases of intra-abdominal intestinal obstruction, has been admirably advocated by Finsterer to avoid the appalling mortality of this rather uncommon catastrophe.

CASES OF PARACÆCAL HERNIA REPORTED SINCE 1925

Moynihan collected records of cases up to 1906, and Rendle Short revised the literature up to January, 1925. The following cases have been collected from 1925 to 1934 :—

Hernia into the Ileo-appendicular Fossa.—

1. MALCOMB[14] (1927).—Male, aged 18. Symptoms of acute obstruction; similar attack three years previously. Diagnosis: Appendicitis. Operation: Reduction—recovery.

2. STITCH[15] (1927).—Age and sex ? Case of strangulation of 2 metres of the ileum in cavity above the cæcum opening by an orifice between the appendix and terminal ileum. Donald, who quotes this case, regards it as an anomalous fossa similar to that in his case (q.v.).

3. TRAUM[16] (1931).—Male, aged 64. Symptoms of acute obstruction. Diagnosis: Acute appendicitis. Operation: Reduction—recovery.

Hernia into the Retrocolic Fossa.—

4. COLEY and HOGUET[10] (1929).—Male, aged 39. Symptoms of chronic abdominal pain for six months, no strangulation. Diagnosis: Retroperitoneal hernia (X-ray negative). Operation: Reduction—recovery.

5. HENNIG[17] (1926).—Female, aged 16. Acute abdominal pain for twenty-four hours; chronic abdominal pain for months previously. Diagnosis: Ovarian lesion. Operation: Resection of bowel—recovery.

6. VIDGOFF and STURGEON[18] (1930).—Age and sex? Symptoms of severe pain and vomiting for twenty-four hours. Diagnosis: Acute appendicitis or obstruction. Operation: Reduction—recovery. Cæcum formed part of hernial contents.

7. LONG[19] (1929).—Male, aged 24. Symptoms of colicky abdominal pain and nausea. Diagnosis: ? Operation: Reduction—recovery.

Hernia into the Fossa Iliaco-subfascialis.—

8. DUNN[6].—This case is mentioned in *Operations of Surgery* by Rowlands and Turner, but no record is available otherwise.

Hernia into Anomalous Openings.—

9. DONALD[20] (1930).—Male, aged 57. Symptoms of four days' central abdominal pain shifting to the right iliac fossa with fæcal vomiting. Diagnosis: Small-intestinal obstruction. Died two hours after operation. Autopsy: 16 in. of strangulated ileum in sac behind mesentery of terminal ileum and internal to the inner border of ascending colon; orifice behind the base of the appendix, which was itself fused with the anterior wall of the sac. Donald suggests that this sac was caused by failure of fusion of the parietal peritoneum with the primitive mesocolon during the terminal stage of development and rotation of the gut.

SUMMARY

1. A case of strangulated hernia into the fossa iliaco-subfascialis has been described in detail.

2. A case of double intestinal obstruction, due to a strangulated hernia through the foramen of Winslow superimposed upon colonic obstruction, has been described.

3. The anatomy and probable causation of the fossa iliaco-subfascialis has been discussed.

4. The symptomatology and diagnosis of paracæcal herniæ have been mentioned, and the results of cases described in the literature have been analysed.

5. The rare but important condition of double intestinal obstruction has been emphasized and the two types of this lesion have been briefly considered.

6. A summary of cases of paracæcal hernia described in the literature since Rendle Short's revision in 1925 has been included.

REFERENCES

[1] FINSTERER, *Wien. klin. Woch.*, 1918, xxxi, 25.
[2] MOYNIHAN, LORD, *Retro-peritoneal Hernia*, 1906, 2nd. ed. London.
[3] SHORT, A. RENDLE, *Brit. Jour. Surg.*, 1915, iii, 48.
[4] BIESIADECKI, *Untersuchungen aus dem path. Anatom.* (quoted by Moynihan).
[5] TARENETZKY, *Institut. zu. Krakau* (quoted by Moynihan).
[6] DUNN, Quoted in Rowlands and Turner's *Operations of Surgery*, 1927, ii, 345. London.
[7] ANDREWS, EDMUND, *Surg. Gynecol. and Obst.*, 1923, Nov., 740.
[8] ATHERTON, *Ann. of Surg.*, 1903, xxxvii, 883.
[9] ROCK CARLING and JONES, *Brit. Med. Jour.*, 1923, ii, 1082.
[10] COLEY and HOGUET, *Ann. of Surg.*, 1929, Oct., 765.
[11] RIESE, H., *Arch. f. klin. Chir.*, 1909, lx, 92.
[12] MANSELL MOULLIN, *Lancet*, 1899, April 1.
[13] SHORT, A. RENDLE, *Brit. Jour. Surg.*, 1925, xii, 45.
[14] MALCOMB, *Canad. Med. Assoc. Jour.*, 1927, xvii, 449.
[15] STITCH, *Zentralb. f. Chir.*, 1927, liv, 3159.
[16] TRAUM, E., *Med. Klinik*, 1931, xxvii, 506.
[17] HENNIG, *Monatschr f. Geburtsh u. Gynäk.*, 1926, April, 73.
[18] VIDGOFF AND STURGEON, *Western Jour. Surg.*, 1930, xxxviii, 702.
[19] LONG, *Ann. of Surg.*, 1929, xc, 157.
[20] DONALD, *Brit. Jour. Surg.*, 1930, xvii, 463.

THE VALUE OF THE UREA-CLEARANCE TEST IN URINARY SURGERY*

By E. W. RICHES
ASSISTANT SURGEON AND ASSISTANT UROLOGIST TO THE MIDDLESEX HOSPITAL,

AND J. DOUGLAS ROBERTSON
CLINICAL CHEMICAL PATHOLOGIST TO THE MIDDLESEX HOSPITAL

THE determination of the renal function in nephritis has received a great deal of attention from workers in all countries, but less attention seems to have been paid to the renal element in urological surgery. The degree of renal function impairment consequent upon prostatic obstruction plays a large part in the immediate risk of prostatectomy. Cohen, Dodds, and Webb[1] drew attention to the necessity of assessing the renal function in operations on the prostate, and suggested the determination of the non-protein nitrogen of the blood. Dukes,[2] as recently as 1934, claimed that the blood-urea was of more value than any other single test in surgical disease of the urinary tract. Van Slyke and his collaborators[3] have, however, shown that the urea-clearance test possesses many advantages over other tests of renal function, so it was decided to employ this test in the present investigation.

Comparison of the urea-clearance test with other tests generally employed may be summarized thus :—

Blood-urea.—Van Slyke has pointed out the disadvantages of employing this figure alone. Further, Mackay and Mackay[4] have shown that the blood-urea does not begin to rise until the kidneys are reduced to half their original functioning power. As a means of assessing renal damage the blood-urea may be said to be of little clinical value, as it depends in part on the protein intake.

Urea-concentration Test.—McLean and De Wesselow[5] drew attention to this test, and it held many advantages over isolated blood-urea determinations. It consisted in collecting specimens of urine every hour for three hours, after a dose of 15 grm. of urea by mouth. The kidneys are considered efficient if urea rises above 2 per cent in any specimen. The objections to this test are the dependence of the result on absorption from the gut and the fact that it is possible to have a high concentration of urinary urea with severe renal impairment, i.e., a very high blood-urea.

Blood-creatinine.—The blood-creatinine has been considered a very good index of renal function, and Holten and Rehberg[6, 7] have discovered a ratio obtained from the rate of creatinine excretion after a dose by mouth. They report good results, but the method of determination of blood-creatinine is a colorimetric one which produces a great error.

---

* From the Urological Department and the Courtauld Institute of Biochemistry, Middlesex Hospital, London, W.1.

Phenolsulphonephthalein.—It has been shown by careful work by Van Slyke that the urea-clearance registers fall in renal function some weeks or months before the phthalein excretion does.

It can be seen that the urea-clearance possesses many advantages over other tests. It is a more delicate indicator of fall in function than the others, and in addition it does not depend upon the excretion of a foreign substance. The kidney is observed working under normal physiological conditions.

EXPERIMENTAL

The cases studied consisted of: (1) Prostatic obstruction; (2) Renal tuberculosis; (3) Renal and ureteric calculi; (4) Hydro- and pyonephrosis; (5) Miscellaneous group.

Technique of Test.—The examination was performed in the morning after breakfast or in the afternoon after lunch. No preparation of the patient was carried out, except that no coffee was taken with the previous meal. The patient was at rest on a chair or couch during the test because exercise had been found to influence the results. Blood was withdrawn a few minutes before the end of the first hour. Patients were instructed not to void urine within three hours of their attendance, because of the uncertainty of emptying the bladder completely when containing only a small amount of urine. During the test the same difficulty of voiding urine was experienced at the end of the hour. This could be partially overcome by giving the patient a glass of water at the beginning and again at the end of the first hour. It was found that if a greater amount than this were drunk, while urination was made easier, there was a tendency to produce too low a urinary urea for accurate determination. It is most important that accurate time intervals be kept, and a stop-watch was employed to ensure accuracy to within a quarter of a minute. The duration of the period need not be one hour; it may be forty-five minutes, provided always the exact time is noted. It has been calculated that an error of one minute in the time interval produces an error of 1 per cent in the final renal function estimate. Another source of error is incomplete emptying of the bladder. It has been our custom to catheterize all women and all prostate cases. An example is shown demonstrating the accuracy of the test when carried out as described above :—

H. J., aged 49. Diagnosis: Carcinoma of kidney.

10–10.02 a.m.—Catheterized and bladder emptied. Specimen discarded.
10.55.—Bled of 5 c.c. of blood.
11.02.—Bladder emptied by catheter (Specimen 1).
12.02.—Bladder emptied by catheter (Specimen 2).
Blood-urea = 30 mgrm. per 100 c.c.

1st Hour.—Urinary-urea = 0·4 grm. per cent = 400 mgrm.
Urine volume = 160 c.c. per hour (2·66 c.c. per minute).

$$\textit{Maximum Clearance } (C_m) = \frac{U}{B} \times V$$

$$= \frac{400}{30} \times 2{\cdot}66 = 35{\cdot}5 \text{ c.c.}$$

Normal is 74 c.c.

$$\therefore \text{ Percentage of normal } = \frac{35{\cdot}5}{74} \times 100 = 47 \text{ per cent of normal.}$$

2nd Hour.—Urinary urea = 0·6 grm. per cent = 600 mgrm. per cent.
Urine volume = 92 c.c. per hour (1·53 c.c. per minute).

$$\textit{Standard Clearance } (C_s) = \frac{U}{B} \times \sqrt{V}$$

$$= \frac{600}{30} \times \sqrt{1{\cdot}53}$$

$$= \frac{600}{30} \times 1{\cdot}24 = 24{\cdot}0 \text{ c.c.}$$

Normal is 54 c.c.

$$\therefore \text{ Percentage of normal} = \frac{24}{54} \times 100 = 44 \text{ per cent of normal.}$$

Mean = 45·5 per cent.

This patient's renal function was only 46 per cent of normal. During the present investigations, results which did not agree within 10 per cent were repeated.

PROSTATIC OBSTRUCTION

From the surgical point of view the importance of having available a reliable test of renal function in cases of prostatic obstruction cannot be overestimated. In this condition any impairment of function is likely to involve the two kidneys equally, and it was therefore hoped that the urea-clearance test might prove of especial value in this connection; it may be stated at the outset that in our opinion this hope has been realized.

Summary of Results.—The test has been successfully carried out upon 70 patients suffering from prostatic obstruction. Of these, 58 have subsequently undergone operative treatment upon the prostate, either by endoscopic resection or suprapubic prostatectomy, and in the latter group the Harris operation has been performed in the more recent cases. The remaining 12 include cases treated by medical means and dilatation and those still undergoing drainage with a view to increasing their renal function, and they are analysed separately.

(Throughout this section the term 'two-stage' is used for cases in which preliminary suprapubic drainage was carried out; cases in which an indwelling catheter was sufficient are classed as 'one-stage' operations.)

Table I sets out the total number of cases treated by each method, with the operative deaths.

Table I.—All Cases Operated Upon

Operation	Number	Deaths
One-stage prostatectomy	21	3
Two-stage prostatectomy	2	1
One-stage endoscopic resection ..	29	1
Two-stage endoscopic resection ..	6	1
Total ..	58	6

The cases treated by resection include 10 cases of prostatic carcinoma.

Table II includes all cases in which the urea-clearance test showed a renal function of not less than 60 per cent at the time of operation.

Table II.—FUNCTION ABOVE 60 PER CENT

OPERATION	No.	WELL	DIED	CAUSE OF DEATH
One-stage prostatectomy ..	19	17	2	1 Heart failure* 1 Pulmonary embolism
Two-stage prostatectomy ..	1	1	–	
One-stage endoscopic resection	24	24	–	
Two-stage endoscopic resection	5	5	–	
Total ..	49	47	2	

* This patient died fifteen minutes after leaving the theatre; no post-mortem was obtained.

Table III includes all cases in which the urea-clearance test showed a renal function of less than 60 per cent at the time of operation.

Table III.—FUNCTION BELOW 60 PER CENT

OPERATION	No.	FUNCTION	WELL	DIED	CAUSE OF DEATH
		Per cent			
One-stage prostatectomy ..	2	52	1	–	
		59	–	1	Prolonged suprapubic fistula, bronchopneumonia
Two-stage prostatectomy ..	1	52	–	1	Uræmia
One-stage endoscopic resection	5	50	1	–	
		55	–	1	Uræmia + sepsis*
		59	1	–	
		55	1	–	
		57	1	–	
Two-stage endoscopic resection	1	48	–	1	Uræmia
Total	9		5	4	

* A case of carcinoma of the prostate with infected hydronephrotic kidneys.

Table IV shows the cases not operated upon. The reasons for not operating upon these patients included poor renal function, insufficient symptoms, and the presence of intercurrent disease.

Table IV.—CASES NOT OPERATED UPON

TREATMENT	NUMBER
Suprapubic drainage ..	6
Medical and dilatation ..	4
Refused treatment	2
Total ..	12

Of the cases drained, two died, one (function 30 per cent) from uræmia, and one (function 85 per cent) from pelvic abscess. Of the remainder, three will

probably come to operation, as their renal function improves, although it has in this series been found that a urea-clearance of 60 per cent is less easily attained after suprapubic drainage than by catheter drainage. This may be due to the fact that the cases submitted to suprapubic drainage are initially in worse condition than the others.

Comparison with other Renal Function Tests.—In all of these cases a comparison is possible between the renal function as estimated by the urea-clearance test and that determined by an estimation of the blood-urea, as a measurement of the latter forms part of the urea-clearance test. In some, various other tests have been performed, such as the urea-concentration test, indigo-carmine test, and a renal X-ray after uroselectan. A few cases may be quoted from the series to illustrate the fallacies of some of the other tests, and in particular the false security into which a blood-urea determination may lead one.

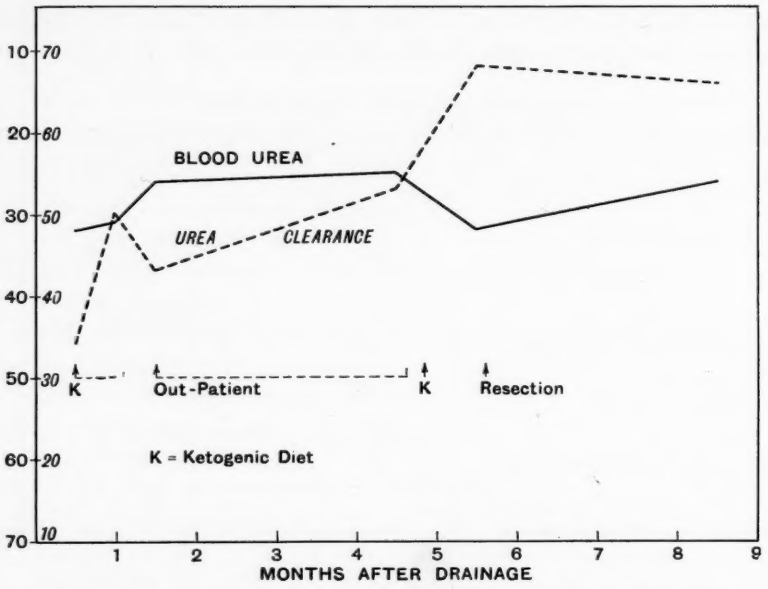


FIG. 86.—*Case* 1. Chart showing blood-urea and urea-clearance findings.

Case 1 (*Fig.* 86).—A. W., aged 58, admitted with acute retention of urine due to a fibrous prostate. The urine was heavily infected and the general condition poor.

The clinical condition showed the need of drainage, and suprapubic cystotomy was done. After a fortnight the blood-urea was 32 mgrm. per cent, but the urea-clearance only 34 per cent. X-rays after uroselectan showed poor secretion from both kidneys with some dilatation of the pelves. A fortnight later with a ketogenic diet for part of the time the urea-clearance rose to 50 per cent, the blood-urea being 31 per cent. The ketogenic diet was withheld for the next fortnight, when the urea-clearance had fallen to 43 per cent, with an improvement of blood-urea to 26 mgrm. per cent. The patient was then discharged from hospital and treated as an out-patient for a further three months, by which time the urea-clearance had risen to 53 per cent, whilst the blood-urea remained fairly constant at 25 mgrm. per cent. He was then re-admitted and given a partial ketogenic diet, and one month later the urea-clearance had risen to 68 per cent, whilst the blood-urea had deteriorated to 32 mgrm. per cent. At this stage endoscopic resection of the prostate was performed and he made an uninterrupted recovery, the suprapubic wound being dry on the eleventh post-operative day. Three months after operation the urea-clearance was 66 per cent and the blood-urea 26 mgrm.

per cent. He now, more than a year after the operation, has no urinary symptoms, no infection, and there is no residual urine.

It is unlikely that this result would have been achieved without prolonged drainage, the necessity for which was only shown by the urea-clearance figures. The blood-urea figures were definitely misleading. The uroselectan pictures also indicated considerable renal damage but did not give an accurate idea of its severity; in another case with a urea-clearance of only 59 per cent uroselectan was excreted in good concentration on both sides, the only abnormality shown being slight dilatation of the pelvis and ureter on the left side. Whilst excretion urography gives a visible indication of renal impairment, it is not sufficiently exact to be used as an index of operability in cases of prostatic obstruction.

Case 2.—E. C. M., aged 68, a diabetic, with prostatic symptoms and more than one pint of residual urine, due to a glandular enlargement of the prostate. The blood-urea was 49 mgrm. per cent; the urea clearance-test was unsatisfactory as the two specimens at intervals of an hour did not agree within 10 per cent. Intravenous indigo-carmine was excreted faintly from each kidney after twenty minutes. Drainage by indwelling catheter was instituted, and after five days indigo-carmine was excreted in poor concentration after eleven minutes. After eight days the urea-clearance was 111 per cent, blood-urea 31 mgrm. per cent, and indigo-carmine was excreted in good concentration at ten minutes. Suprapubic prostatectomy by the Harris technique was performed on the tenth day, and progress was uneventful. The suprapubic wound remained dry, and urine was passed naturally when the urethral catheter was removed on the tenth post-operative day.

In this case the indigo-carmine test gave a reliable indication of renal function, but it is not so accurate as the urea-clearance; the estimation of depth of colour is not easy unless a standard is available for comparison. The test, however, has the advantage of being easily carried out at the bedside and of being interpreted immediately. It therefore forms a useful check during the period of drainage to indicate when another clearance test should be performed.

Case 3.—E. P., aged 70, admitted with symptoms due to a glandular enlargement of the prostate. Drainage by indwelling catheter was instituted and tests of renal function were carried out. The blood-urea was 56 mgrm. per cent, urea-clearance 30 per cent, and the urea-concentration test showed 1·3 per cent in the first specimen, 1·4 per cent after one hour, and 1·9 per cent after two hours. In view of the unsatisfactory results of these tests, suprapubic cystotomy was performed, but the patient gradually went into uræmia and died three days afterwards in coma.

In this case all three tests showed a serious impairment of renal function, but the urea-clearance test gave the most certain indication of the extremely grave prognosis.

The urea-concentration test is undoubtedly of value in these cases, but apart from the fallacies which have already been pointed out it suffers from others; for example, it is interpreted differently by different observers, and whilst some would consider a high initial urea value essential for good function, others would look on a high range of increase as of more importance.

Effect of Drainage.—It has been pointed out that infection plays a large part in depressing renal function, and drainage alone, whether by suprapubic tube or indwelling catheter, will do little to combat infection and may even increase it unless other measures are applied to overcome it. The lowest value for the urea-clearance in this group was 29 per cent; this patient (G. C.), whose urine was infected, was sent out after suprapubic cystotomy, and after fourteen months'

drainage and treatment as an out-patient his function is only 49 per cent. In another case (R. E.), admitted with a suprapubic cystotomy done elsewhere some months previously for prostatic carcinoma, the function on admission was 42 per cent, the urine being infected. After eleven days' in-patient treatment on forced fluids, urinary antiseptics and frequent lavage, the function had risen to 64 per cent, and it was then possible to carry out endoscopic resection; the fistula closed and he was restored to urinary comfort.

The greatest increase after drainage was 56 per cent; in this patient (J. H.), who had over a pint of residual urine and a large glandular prostate, the urea-clearance on admission was only 35 per cent and the urine not infected. After six days' drainage by indwelling catheter it had risen to 91 per cent and a one-stage prostatectomy was performed. Drainage by a urethral catheter appears to be particularly effective in restoring impaired renal function in cases where there is no urinary infection; adequate steps must be taken to prevent the ingress of infection via the catheter, and we now employ a modified Duke's apparatus as a routine for all cases in which an indwelling catheter is necessary for any purpose, so that frequent antiseptic irrigations can be easily carried out. Drainage by suprapubic cystotomy was necessary in only 7 cases out of the 52 who have undergone operations on the prostate, although it is still proceeding in four others, and two died after drainage alone (*see Table IV*).

The Safety Level of Renal Function in Prostatic Cases.—It is necessary to have some standard value of renal function below which operations on the prostate itself, apart from drainage operations only, should not be undertaken, and above which such operations may be safely undertaken, due consideration being given to other factors in the clinical condition of the patient which might influence the result. After a short experience of the test, the figure of 60 per cent was taken arbitrarily as the lower limit of safety. If the urea-clearance test shows a renal function of less than 60 per cent, no operation is undertaken on the prostate until the function has been raised to this figure by catheter or suprapubic drainage. The figure chosen is possibly rather too high, and in the absence of other complications 55 per cent would probably give an adequate margin of safety. At the same time it may be stated that no deaths from uræmia have occurred after prostatic operations where the function reached 60 per cent, whilst there were three deaths in which uræmia played the most important part in cases where the pre-operative renal function was less than 60 per cent. In some cases of death after prostatectomy it is impossible to assess the relative importance of uræmia and infection as causes of the fatal issue; the two factors appear to be intimately connected, for an infected kidney is more likely to fail and a damaged kidney is more easily infected. The urea-clearance test appears to bear this out, as it has been noticed that those cases in which there is urinary infection tend to have a lower renal function than the non-infected cases. It has also been noticed that cases that were operated upon when the renal function was very near 60 per cent have tended to have a more stormy and prolonged convalescence than those with a higher figure.

Some criticism of our interpretation of these results may be made on the grounds that many of the patients were treated by endoscopic resection, a procedure which carries less risk than prostatectomy. It is, however, quite certain that an adequate renal function is just as necessary for the one operation as the other;

one case treated in the days before we used the urea-clearance test as the criterion of operability illustrates this point forcibly :—

E. G. H., aged 88, had lived a catheter life for two years on account of prostatic enlargement, and catheterization was becoming increasingly difficult; there was residual urine amounting to 14 oz. and the blood-urea was 57 mgrm. per cent. After six weeks' suprapubic drainage, the blood-urea had fallen to 43 mgrm. per cent; this was considered a safe level, and endoscopic resection was carried out without difficulty. After operation he secreted no urine, and within fourteen hours was in coma. Thirty-one hours after operation he died. This death was purely uræmic, and had we been using the urea-clearance at that time, he would probably never have been operated upon.

To summarize the results in cases of prostatic obstruction we would state that, whilst the clinical condition of the patient is the ultimate deciding factor in assessing the operability, assistance from laboratory tests is necessary to tell us when the renal function is sufficiently good to allow an operation on the prostate to be carried out in safety. Of the tests used, we have found the urea-clearance test to be the most reliable; the urea-concentration test has not given such accurate information in the borderline cases; estimation of the blood-urea only shows extreme degrees of renal impairment, and may be misleading; excretion urography demands such standardization of X-ray technique as to make it unsuitable for general application; excretion of indigo-carmine is a useful bedside test, but its interpretation is not sufficiently accurate for borderline cases.

The insistence on a urea-clearance of 60 per cent may result in the withholding of the benefits of operation from a small number of cases, but it is undoubtedly a potent factor of safety for the majority. The adoption of this standard has already effected a considerable lowering of the mortality of operations on the prostate in this hospital.

At the beginning and throughout the investigation, the urea-clearance test was carried out in a number of surgical renal conditions. It was found after a time that whilst the results were of considerable interest, they were not of such value to the surgeon as in the prostatic cases; in consequence the test was not adopted as a routine, and hence the number of cases in each group is relatively small. In several cases where the urea-clearance was low, the test has been repeated at intervals after the operation, and in this way some facts of importance in prognosis have been brought to light.

The conditions investigated are classified into the following groups: (1) Renal tuberculosis; (2) Renal or ureteric calculus; (3) Hydronephrosis and pyonephrosis; (4) Miscellaneous affections of the kidneys and bladder.

RENAL TUBERCULOSIS

Twelve patients with proved renal tuberculosis have been investigated before operation, and in addition four patients who had undergone nephrectomy for this condition at varying intervals before, have been tested. *Table V* gives the details of the cases investigated pre-operatively; as well as the urea-clearance it includes the blood-urea figures, the presence or absence of secondary infection of the urine, the findings on excretion urography with either uroselectan or abrodil, an estimate of the degree of kidney damage found at operation, and notes on the subsequent progress of the case. The cases are arranged in the order of their urea-clearance values, starting with the lowest.

Table V.—RENAL TUBERCULOSIS

PATIENT	SEX AND AGE	UREA-CLEARANCE	BLOOD-UREA	S.I.*	EXCRETION UROGRAPHY	KIDNEY DAMAGE FOUND AT OPERATION	PROGRESS
		Per cent					
1. L. D.	M. 14	18	54	0	Dilatation of both pelves	No operation (Bilateral)	Died 1 year later
2. L. P.	F. 23	33	27	0	Calcification. Normal pelvis	Moderate	Clearance rose to 103 per cent after 8 months. Well 18 months later
3. E. F.	F. 23	35	32	0	Filling defect	Extensive	Clearance fell to 32 per cent. Well 12 months later
4. H. D.	F. 29	56	30	0	Dilatation of pelvis	Extensive	Well
5. E. P.	F. 34	56	30	0	Poor concentration	Moderate in upper half of double kidney Lower normal	Well
6. W. C.	M. 55	57	26	0	Poor concentration. Other kidney enlarged	Extensive	Bilateral infection. Died of uræmia 13 months later
7 R. N.	F. 16	60	37	0	No excretion on affected side	Moderate	Clearance rose to 83 per cent after 8 months. Well 27 months later
8. J. P.	F. 28	70	29	*B. coli*	Filling defect	Moderate	Well 20 months later. Clearance fell
9. E. D.	F. 31	70	22	0	Dilatation. Calcification	Slight	Clearance rose to 98 per cent after 1 month. Well
10. J. G.	M. 45	100	28	0	Dilatation of ureter	Slight	Well 12 months later
11. L. C.	M. 30	100	25	0	Filling defect	Slight	To sanatorium for pulmonary infection
12. A. B.	M. 23	120	24	0	No excretion on affected side	Slight	Well 5 months later

* S.I. = Secondary infection.

It will be seen that the lowest urea-clearance in the series was 18 per cent; this was in a boy with extensive bilateral involvement on whom no operation was performed and who died subsequently. In one other case (*Case* 6) bilateral infection was suspected, and it became manifest within a year of nephrectomy; the urea-clearance in this case was 57 per cent and the patient died of uræmia thirteen months after operation. All the other patients are known to be alive and well.

The lowest urea-clearance at which nephrectomy was successfully performed was 33 per cent (*Case* 2), and in this case it rose to 103 per cent eight months after operation, a fact which was in full agreement with the satisfactory clinical condition. *Cases* 7 and 9 also showed a considerable rise in function after the offending kidney had been removed. In two cases there was a fall in the urea-clearance value after operation. In *Case* 3 the figure was 35 per cent before operation and 32 per cent six months later, but whilst originally there was no secondary infection, on the second occasion there was a definite *B. coli* infection of the urine. The other case in which there was a diminution in the urea-clearance value after operation (*Case* 8)

had a secondary *B. coli* infection at the time of operation; in her case the test was repeated at intervals for a year with the following results:—

Interval	Urea-clearance Per cent	Blood-urea Mgrm. per cent
Pre-operative	70	29
1 months	70	24
3 months	35	31
12 months	63	21

It seems fair to presume that the secondary infection was the deciding factor in preventing the rise in function after the removal of a diseased kidney which the other cases led us to anticipate.

The blood-urea figures show that only in the case where the urea-clearance was only 18 per cent was the blood-urea raised above what is commonly accepted as normal; an isolated estimation of the blood-urea appears to be of value only in the extremes of renal dysfunction.

Excretion urography was frequently of considerable help in confirming which was the affected side, but gave no clear idea of the amount of renal damage. If the ureter is blocked from any cause, it would appear that there may be no excretion of the dye on that side; this occurred in two cases (*Cases* 7 and 12), in which at operation only moderate or slight renal damage was found, but in which the X-ray picture was identical with that obtained in complete destruction of all the secreting tissue.

The extent of the destruction of the kidney substance found at operation is classified as extensive, moderate, or slight, and it will be seen that this degree of damage is forecast more closely by the urea-clearance test than by any other of the tests employed.

The indigo-carmine test was performed in some cases, but with this also there was no indication of the degree of destruction in the moderately damaged cases.

From the surgical point of view, the most important conclusion to be drawn is that when the infection is confined to one kidney nephrectomy is usually safe whatever the total renal function may be; provided that there is no secondary infection, the function as estimated by the urea-clearance test will probably show an improvement after removal of the diseased kidney.

Table VI shows the results of the test in four cases investigated at varying intervals after nephrectomy for tuberculosis; in each case the patient is alive at present and apparently well.

Table VI.—Results after Nephrectomy

Interval after Nephrectomy	Urea-clearance
	Per cent
14 months	70
5 years	40
5 years	43
10 years	62

RENAL AND URETERIC CALCULI

The test was performed in 10 cases of stone in the upper urinary tract; 01 these, 6 were unilateral and 4 bilateral. The results are given in *Table VII* together with the relevant clinical data.

Table VII.—RENAL AND URETERIC CALCULI

PATIENT AND AGE*	SITE	UREA-CLEARANCE	BLOOD-UREA	S.I.†	EXCRETION UROGRAPHY	PROGRESS AFTER OPERATION
Unilateral.—		Per cent				
1. J. G. 59	U.	62	55	*B. coli*	Normal	Diabetic. Well
2. L. R. 38	U.	80	39	0	Slight hydronephrosis	Well
3. S. D. 38	U.	80	28	0	Slight hydronephrosis	Clearance rose to 98 per cent after 1 month
4. A. R. 52	U.	80	30	0	—	Tested 4 years after passing stone
5. S. J. 43	K. Pelvis	90	31	0	—	Well 3 years later
6. C. S. 34	U.	100	27	0	—	Well 18 months later
Bilateral.—						
7. E. H. 29	K. Pelvis	56	34	0	—	Multiple calculi
8. H.B. 52	K. and U.	62	26	0	L., slight hydronephrosis; R. considerable hydronephrosis	L. renal and ureteric R. multiple stones and papillary adenocarcinoma
9. A. H. 38	K. Pelvis	65	36	*Staph.*	Bilateral hydronephrosis	Extensive renal damage
10. M. A. 49	K. Pelvis	82	42	*B. coli*	R. hydronephrosis	Fairly well. No operation

* All these cases were males, and all were treated surgically except *Cases* 4 and 10.
U = Ureter; K = Kidney. † S.I. = Secondary infection.

In the cases of unilateral calculi the urea-clearance was 80 per cent or more in all but one, and this was the only case with infection. Improvement after removal of the stone was recorded in the only case in which the test was repeated.

In the bilateral cases the clearance was below 66 per cent in all but one; this patient has a surprisingly good renal function. He has a history of stone extending back for twenty-five years, and there are now multiple branching calculi in the right kidney and a single one in the left. Both kidneys concentrate uroselectan fairly well, although the right is hydronephrotic; indigo-carmine is excreted from the right side in four and a half minutes, and from the left in four minutes, in keeping with a urea-clearance of 82 per cent. The patient declined to consider operation and has been treated for four years by urinary antiseptics and bladder lavage.

HYDRONEPHROSIS AND PYONEPHROSIS

This group includes six cases. *Table VIII* sets out the clinical and laboratory findings.

In this group again the fact that infection is a potent factor in lowering renal function is well illustrated. It is also made evident that where one kidney is completely atrophied, the total function may still be approximately normal, provided there is no infection. In *Case* 4 the right kidney failed to secrete uroselectan and was found at operation to consist of a fibrous hydronephrotic shell with scarcely any renal substance, yet the clearance was 93 per cent. In *Case* 5 there was very poor concentration of uroselectan, and no excretion of indigo-carmine after twenty minutes, yet the clearance was 100 per cent. After the removal of an infected kidney, or the correction of an obstructed ureter, the function tended to rise.

Table VIII.—HYDRONEPHROSIS AND PYONEPHROSIS

PATIENT	SEX AND AGE	CONDITION	UREA-CLEARANCE	BLOOD-UREA	S.I.*	TREATMENT	PROGRESS
			Per cent				
1. E. C.	M. 36	R. pyonephrosis. Vessel crossing ureter	35	37	+	Nephrectomy	Clearance rose to 50 per cent after 1 month, and 74 per cent after 10 months
2. R. R.	M. 34	R. hydronephrosis. Probably congenital	65	39	+	Plastic operation	Clearance rose to 74 per cent after 1 year
3. J. P.	M. 54	Stricture of urethra. R. pyonephrosis. L. hydronephrosis	75 after R. nephrostomy	28	+	R. nephrostomy. Dilatation of stricture	Eight months later L. pyonephrosis. Died of uræmia after L. nephrostomy
4. A. B.	M. 23	R. hydronephrosis	93	37	0	Nephrectomy	Complete destruction of renal tissue. Clearance 95 per cent after 4 months
5. L. P.	F. 40	R. hydronephrosis; L. slight dilatation	100	19	0	R. plastic operation	Indigo-carmine—L. 4 mins., R. 0, (before operation)
6. D. D.	M. 36	L. hydronephrosis	100	22	0	Plastic operation	Well 6 months later

* S.I. = Secondary infection.

MISCELLANEOUS GROUP

The urea-clearance test was also carried out in a number of other surgical urological conditions which are shown in *Table IX*.

Table IX.—MISCELLANEOUS

PATIENT	SEX AND AGE	CONDITION	UREA-CLEARANCE	BLOOD-UREA	S.I.*	NOTES
			Per cent			
1. H. J.	M. 49	Carcinoma of R. kidney	46	30	+	Large tumour removed by abdominal nephrectomy. Clearance rose to 66 per cent after 1 month and 84 per cent after 5 months
2. F. S.	F. 58	Pyelitis	65	44	*B. coli*	—
3. B. S.	F. 58	R. pyelonephritis	70	40	+	Nephrectomy
4. F. M.	F. 47	Ureterocele	89	19	0	Removed by cystodiathermy
5. G. W.	M. 69	Carcinoma of bladder	100	30	*Staph.*	Growth did not involve ureter
6. W. E.	M. 65	L. renal tumour	100	27	0	Poor excretion of uroselectan. Refused operation
7. M. C.	M. 24	L. lumbar abscess	102	27	0	Pott's disease of spine. Kidney displaced by abscess

* S.I. = Secondary infection.

In *Case* 1 the depression of renal function was probably due to the infection, and its subsequent rise to the removal of the infected growth; in *Case* 6 a non-infected growth showed a clearance of 100 per cent.

SUMMARY

1. The urea-clearance test is discussed, and the technique employed is described.

2. The results of the test in 109 surgical cases are tabulated.

3. The presence of urinary infection lowers the clearance value.

4. The test is reliable as an index of operability in prostatic obstruction; where the urea-clearance is over 60 per cent, operation is safe, whilst below this figure it is hazardous.

5. In unilateral lesions of the upper urinary tract, the total renal function is of little importance; it improves after removal of the underlying cause, and a normal urea-clearance may be attained with only one kidney.

Our thanks are due to our colleagues at Middlesex Hospital who have allowed us to include some of their cases, to Professor E. C. Dodds for his encouragement in this investigation, and to Mr. Webb-Johnson for his criticism and advice.

REFERENCES

[1] COHEN, I., DODDS, E. C., and WEBB, C. H. SHORNEY, *Brit. Jour. Surg.*, 1926, xiii, 656.
[2] DUKES, C., *Proc. Roy. Soc. Med.* (Urol. Sect.), 1934, xxvii, 657.
[3] VAN SLYKE, D. D., et al., " Observations in the Course of Different Types of Bright's Disease and on Resultant Changes in Renal Anatomy ", *Medicine*, 1930, ix, 257.
[4] MACKAY, E. M., and MACKAY, L. L., " The Relation between Blood-urea Concentration and the Amount of Functioning Renal Tissue ", *Jour. Clin. Invest.*, 1927, iv, 127.
[5] MCLEAN, H., and De WESSELOW, O. L. V., *Brit. Jour. Exper. Pathol.*, 1920, iii, 53.
[6] HOLTEN, C., and REHBERG, P. B., *Acta med. Scand.*, 1931, lxxiv, 479.
[7] HOLTEN, C., and REHBERG, P. B., *Ibid.*, 538.

THE EFFECT OF TRACHEAL OCCLUSION ON THE HYPERTROPHY OF THYROID TRANSPLANTS AND REMNANTS

By E. WALTER WORKMAN and G. GAVIN MILLER
FROM THE DEPARTMENT OF EXPERIMENTAL SURGERY, McGILL UNIVERSITY, MONTREAL, CANADA

INTRODUCTION

The present work was carried out in order to study more closely the causes producing histological changes in the thyroid gland. The importance of iodine as a factor in producing thyroid gland changes was evident, but was not, apparently, the only factor. Breitner considered iodine was the controlling factor and that it tended to bring both the hyperactive and hypoactive gland back to the normal phase. In the present experiments identical changes were produced without directly interfering with iodine metabolism. Since this work was begun two years ago, the important work of Collip, demonstrating the presence of both thyreotropic and antithyreotropic hormones in the blood-stream, has been published. He has further demonstrated that these hormones maintain a balance, which he explains by his theory of " inverse response ". To-day it would seem that bodily requirements for thyroxine upset the balance between thyreotropic and antithyreotropic hormones, thus increasing or decreasing the demand for thyroxine. Depending on the need for thyroxine the gland becomes hyperplastic, or goes into the resting phase. Iodine, as the most important constituent of thyroxine, has a definite place in this cycle. When one whole lobe of the thyroid gland and two-thirds of the other are removed from animals the remnant becomes hyperplastic. The remnant, having to do the work of the whole gland, is stimulated to activity, and hyperplasia results. Four or five months later, hypertrophy having resulted, stimulation stops and the gland again shows essentially normal structure histologically, though there may be traces of hyperplasia still remaining.

Breitner has shown that partial tracheostenosis produces a gland of low activity with increased colloid, the so-called resting phase.

Two simple mechanical means are consequently available to alter the histological picture of the thyroid at will—one, subtotal thyroidectomy, producing hyperplasia in the remnant; and the other, artificial tracheostenosis, producing a hypoactive gland.

The experiments to be described aim to produce, by means of partial tracheostenosis, a transition in the neck remnant left after subtotal thyroidectomy from the hypertrophic to the colloid phase; further to produce, if possible, identical changes in autotransplants. Breitner had not shown that tracheostenosis would produce the colloid phase in autotransplants as well as in the gland proper.

Such histological changes, if produced, suggest that the body requirements for thyroxine are altered by these experimental methods. If the autotransplants

showed identical changes, then it would follow that these changes must be due to a blood-borne factor—in other words, a hormone—and that this hormone was, to a certain extent at least, controlled by body requirements.

In this case the important position given to iodine in thyroid changes would need careful review. It could no longer be considered the controlling factor in thyroid function, but rather one in a chain of interrelated factors. Collip has since shown that such other factors do exist—namely, thyreotropic and antithyreotropic hormones.

HISTORICAL REVIEW

In 1919 Loeb[1] studied the structural changes in the thyroid gland of the guinea-pig after removal of from one-half lobe to more than one and two-thirds lobes of the gland. He concluded: (1) After removal of half of one lobe no definite changes occurred; (2) After removal of one lobe slight hypertrophic changes were noticed; (3) After removal of one and one-half lobes definite hypertrophic changes occurred; (4) After almost complete removal of both lobes marked changes were found in the remnants. These compensatory hypertrophic changes developed from the fifteenth to the eighteenth day after operation. Cell multiplication ceased from the twenty-second to the thirtieth day. Six to eight weeks after operation there was a new formation of colloid. There was still some evidence of hypertrophy four to five months after operation. The mitotic figures were most marked from the fifteenth to the seventeenth day after operation; subsequently they gradually decreased in number. He observed that hypertrophy was more marked when the animal gained weight,[1, 3] and during the colder months.[4, 6]

Loeb also showed that potassium iodide[4, 6, 8] intensified the compensatory hypertrophic changes, while thyroid, thyroxine, and anterior pituitary substance,[5-7] when given orally, had an inhibitory effect. The intraperitoneal injection of acid or alkaline extract of the anterior pituitary[9] into normal guinea-pigs produced a very intensive hypertrophy of the thyroid with a relative loss of weight. He suggested that this might be due to increased thyroid secretion discharged into the blood-stream, thus raising the metabolism.

In 1903 Cristiani[10] observed that compensatory hypertrophy occurred in thyroid autotransplants. In 1920 Loeb[2, 3] showed that the frequency, character, and degree of hypertrophy were similar in both remnants and autotransplants. Cristiani[11] concluded that structural changes in the transplanted glands were identical with those occurring in the thyroid of the host.

In 1912 Reich and Blauel[12] observed that, following partial tracheostenosis, the thyroid gland of the rat showed histological changes of a colloidal nature. These findings were confirmed by Breitner and Orator[13] in 1924. They studied the changes in gland structure in the rat following: (1) Removal of one lobe of the thyroid; (2) Tracheostenosis; (3) Tracheostenosis and removal of one lobe. They found that after removal of one lobe the other lobe became hyperactive; following tracheostenosis alone the gland became hypoactive; following removal of one lobe together with tracheostenosis, a balance appeared to be obtained and very little change was noted. The stimulation produced by extirpation of one lobe of the thyroid was apparently counterbalanced by the inhibiting effect of partial tracheostenosis. Breitner interpreted these changes as due to a storing up or flushing out of colloid in response to a demand for an increased or decreased metabolism from

the body. Breitner[14] then administered iodine to the rats after hemithyroidectomy and after partial tracheostenosis; in the former the colloid did not disappear, while in the latter there was no increase of colloid. He considered that iodine had the power to inhibit the hyperactive gland and to stimulate the colloidal type. Since this was supported by clinical experience correlated with histological studies, Breitner concluded that iodine was the controlling factor in these histological changes, tending to keep the gland normal.

Carrari,[15] reporting the work of Silvagni in 1931, recorded that, following inhalation of asphyxiating gases, the thyroid gland showed an enlargement of the alveoli, flattening of the epithelium, and an increase in colloid.

Unknown to the authors, Abbott et al.[16] in 1933 repeated Breitner's work, using dogs, pups, and kittens. They showed that the thyroid in young animals is normally hyperplastic, and that tracheostenosis will cause a reversion of the hyperplastic gland to the colloidal type. They concluded that tracheal compression due to a large goitre played no part in the colloidal type of goitre found in these cases. Reich and Blauel, and Breitner, considered these colloidal changes were due to lack of oxygen. Abbott and his co-workers doubted this explanation and concluded that the problem was much more complex.

Collip and his co-workers have made important observations on the thyroid changes occurring in hypophysectomized rats after the injection of anterior pituitary extracts. In 1933 Anderson[17] showed that when an alkaline extract of anterior pituitary was injected into the rat only negligible changes were produced in the thyroid; when the extract was injected together with *Staphylococcus aureus* vaccine a marked hyperplasia occurred with a coincident rise in metabolism. Loeb and Bassett,[9] Krogh,[18] and Baumann and Marine,[19] have all reported thyroid hypertrophic changes in dogs, rabbits, and guinea-pigs as a result of the injections of extracts of the anterior pituitary lobe.

Later in 1933 Anderson and Collip[20] isolated a purified extract of the anterior pituitary lobe containing the thyreotropic factor. Following hypophysectomy the rat thyroid shows marked colloid changes. This is transformed to the active cellular state by the injection of the purified thyreotropic extract. Coincident with this, Anderson and Collip[21] found a marked rise in the metabolic rate. In hypophysectomized rats the metabolic rate fell on an average to 74 per cent of the normal.

Further investigations by Collip and Anderson[22] demonstrated that when these injections are repeated over a prolonged period the metabolic rate again falls and cannot be increased by further injections or by transplanting normal thyroid glands. The serum of these rats was found to contain an antithyreotropic factor.

In March, 1934, Collip[23] explained these findings by his theory of "inverse response". Normally there is a balance between the thyreotropic hormone and the antithyreotropic substance. In hypophysectomized rats the thyreotropic hormone is absent, while the antithyreotropic factor is diminished, as is evidenced by the increased sensitivity of the animal to the thyreotropic extract. The level of a hormone is apparently inversely proportioned to the level of its corresponding anti-hormones. Thus a hyperhormone state, associated with lowered response to injected hormones, implies the coexistence of a hyper-anti-hormone state.

Anderson and Collip[24] have not as yet found where the antithyreotropic substance originates, although they have isolated it from the blood serum.

Loeb and his co-workers[25] demonstrated that the acid extract of the anterior pituitary lobe induced an increase in the organic blood iodine at the expense of the organic iodine content of the thyroid gland. This was accompanied by a marked decrease in thyroid colloid. He concluded that the acid extract caused a diminution of the iodine of the thyroid.

METHODS

In the following experiments adult male and non-pregnant female guinea-pigs were used, since Loeb[1] has stated that these animals under normal conditions do not develop goitre. The previous work of Loeb and Breitner was first repeated in order to confirm their findings.

Ether anæsthesia was used throughout the experimental work. The skin was shaved and sterilized with mercurochrome. In all, 98 animals were used and 194 operations were performed. The partial ligature of the trachea in such a small animal always afforded some difficulty; when the ligature was drawn too tightly, the animal died in a few hours; if it was not tight enough, no changes occurred in the gland. In a few cases the ligature cut through the trachea, and a localized abscess developed. These animals were discarded. Attempts to pass a fine catheter down the trachea and to tie a ligature around it proved unsuccessful. Finally, the ligature was tied to a degree determined by experience. In every case the results of this method were verified by autopsy. The trachea was found to be stenosed to about one-quarter of its normal diameter in those cases which showed histological changes in the gland. Autotransplants, when used, were placed in the subcutaneous tissue of the abdominal wall.

Records of the weights of the animals were kept. The experiments were carried out during the colder months. A preliminary section was taken of each animal's thyroid gland as a histological control. Tissues were fixed in Zenker's solution immediately after extirpation. Paraffin sections were made and stained by the hæmotoxylin-eosin method

Throughout this work Loeb's[5] classification for estimating the degree of hypertrophy has been used. This classification depends on the shape of the acini, the type of cells, the amount of colloid, the presence of granules, and the appearance of mitotic figures. Loeb divides these changes into five gradations: Grade I, showing the greatest degree of hypertrophy, whilst Grade V shows normal structure (*Table I*).

The following criteria for the colloidal phase were adopted: (1) Acini were regular and generally larger than normal; (2) Acini cells were flattened or cuboidal; (3) Granules were indistinct; (4) Mitotic figures were absent; (5) The colloid was increased, filling the lumen of the alveoli.

It had been hoped to carry out metabolic rates, but the necessary apparatus was not available. Efforts were made to determine the oxygen tension of the blood before and after partial tracheal occlusion. An amount of blood sufficient to make these determinations by the usual methods could not be obtained from the guinea-pig; the apparatus for micro methods was not available. It had been hoped to study the hæmatological changes occurring during these experiments; although many hæmograms were studied, the results were so indefinite that this feature of the work was discontinued.

Table I.—Loeb's Classification of Hypertrophic Changes in Thyroid Gland (Modified)

	Degree	Acini	Cells	Granular	Colloid	Mitotic Figures
Grade I ..	Highest	Irregular with papillæ	High columnar	Very distinct	Absent	Present
Grade II ..	Marked	Slit-like and irregular	High columnar	Distinct	Mostly absent Vacuolar	Present
Grade III ..	Decided	Somewhat irregular Some slits	Low columnar	Distinct	Diminished Vacuolar	Present
Grade III to IV ..	Moderate	Slightly irregular	Low columnar	Distinct	Soft, bluish Somewhat diminished	Present
Grade IV ..	Very moderate	Regular, occasionally irregular	Somewhat enlarged	Present	Some softening	Rare
Grade IV to V ..	Trace	Regular	Larger than normal	Indistinct	Solid with early vacuolization	Rare
Grade V ..	Normal	Regular	Flat to cuboidal	Indistinct	Solid Retracted	Very rare

EXPERIMENTS

Experiment I: *Production of Compensatory Hypertrophy following Extirpation of One and One-half to One and Three-quarter Lobes of the Thyroid Gland.*—Eleven guinea-pigs were used. Fifteen to nineteen days after the extirpation of from one

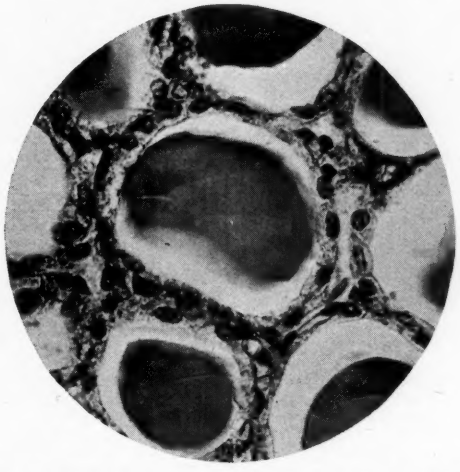


Fig. 87.—Normal thyroid gland of guinea-pig. Acini are regular. Epithelium lining the acini is low, cuboidal; some epithelial cells are flattened. Granules indistinct. Colloid is solid and retracted. (× 400.)

and one-half to one and three-quarter lobes of the thyroid gland, the remnants were removed and sectioned (*Fig.* 88), and were compared with sections taken at the first operation (*Fig.* 87). The remnants all showed varying degrees of hypertrophy, from a trace (Grade IV–V) to marked hypertrophy (Grade II). Six of the animals gained weight, three showed a moderate loss, and in two a slight loss was noted. In the higher grades of hypertrophy the acini were irregular, sometimes slit-like in form. In many acini papillæ were seen. The epithelial cells were high and wide with distinct granules and many mitotic figures; the colloid was softened, vacuolar, diminished, and in some absent; lymphocytes were increased.

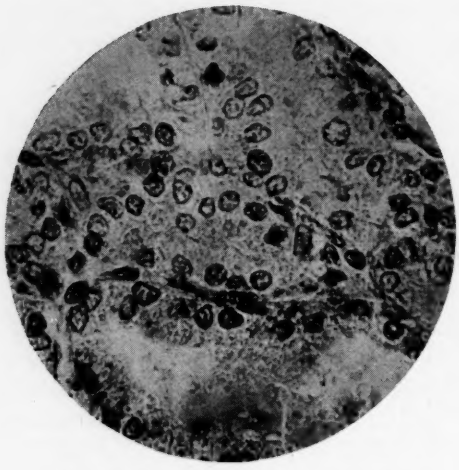


FIG. 88. — Compensatory hypertrophy in neck remnant (Guinea-pig 38). Acini are irregular; some are converted into slits. Epithelial cells are high and wide. Granules are distinct. A mitotic figure may be seen in the section. Colloid is diminished and soft, while some of the alveoli contain no colloid. This section shows marked hypertrophy (Grade II). (× 400.)

EXPERIMENT II: *Compensatory Hypertrophy in Remants and Autotransplants.*— In seven guinea-pigs from one and two-thirds to one and three-quarter lobes of the thyroid gland were extirpated. One lobe was transplanted into the subcutaneous tissue of the abdominal wall; the remainder was sectioned to serve as a control. After fifteen to twenty-one days the animals were sacrificed. Three of the animals showed a gain in weight,

FIG. 89.—Compensatory hypertrophy in remnants and auto-transplants: neck remnant (Guinea-pig 84). Acini are irregular. Epithelial cells are high and wide; granules distinct. Colloid is markedly diminished and soft. Decided hypertrophy (Grade III). (× 400.)

FIG. 90.—Compensatory hypertrophy in remnants and auto-transplants: autotransplant (Guinea-pig 84). Some of the acini are irregular; some show slits. Epithelial cells are high and wide. Mitotic figures are seen in the section. Granules are distinct; colloid is markedly diminished and in some alveoli absent. Decided hypertrophy (Grade III). (× 400.)

while four showed a moderate loss. In six of the animals the grades of hypertrophy in remnants and autotransplants were similar; in one there was moderate hypertrophy (Grade III–IV) in the transplant but none in the remnant. The hypertrophic changes in remnant and autotransplant are shown in *Figs.* 89, 90. The acini are irregular, with papillæ. The epithelial cells are high and wide, with distinct granules and many mitotic figures. The colloid is diminished to absent. Lymphocytes are increased.

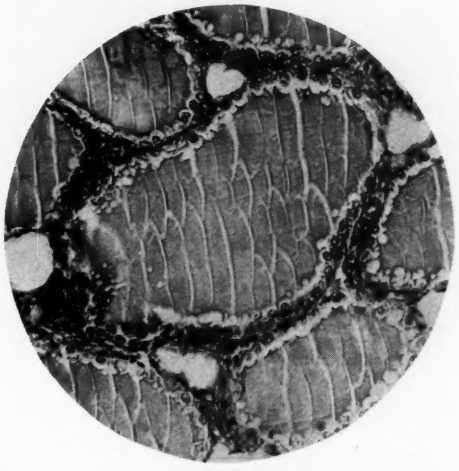


FIG. 91.—Colloidal phase in neck remnant (Guinea-pig 15). Acini are large. Epithelial cells are flattened; granules indistinct; no mitotic figures. Colloid fills the entire lumen. (× 90.)

EXPERIMENT III: *Colloidal Phase in the Thyroid as a Result of Partial Tracheostenosis.* — Four successful experiments were carried out. A small portion of the normal thyroid was first removed as a histological control, the trachea was then partially stenosed by a silk ligature. When the animals were sacrificed ten to eleven days later, in all there was a stenosis of the trachea to about one-fourth of its normal diameter. In three of the animals the body weight was constant, while one showed a marked loss. The thyroid was then sectioned, and in each case the colloidal phase was noted (*Fig.* 91). The acini were much larger than the normal, with flattening of the epithelial cells; mitotic figures were absent, and the granules indistinct. The alveoli were filled with colloid which, for the most part, took the eosin stain readily, although occasionally it assumed a light violet colour suggesting a new formation of colloid.

A number of guinea-pigs were used; in some instances the animals died from asphyxiation due to tightness of the ligature; in some examination at autopsy showed insufficient stenosis, so that gland changes had not occurred; while in others there was cutting through of the ligature with infection. All these animals were discarded.

FIG. 92.—Simultaneous tracheostenosis and subtotal thyroidectomy (Guinea-pig 25). Normal thyroid (control). (× 400.)

EXPERIMENT IV: *Thyroid Changes following Simultaneous Tracheostenosis and Subtotal Thyroidectomy.*—In five guinea-pigs subtotal thyroidectomies and simultaneous tracheostenosis were carried out. After thirteen to eighteen days the animals were sacrificed. In two instances there was a prominence of the colloidal phase, while in three there was hypertrophy (*Figs.* 92–94). The weights were fairly constant; one in which the colloidal phase predominated showed a gain of 147 grm.

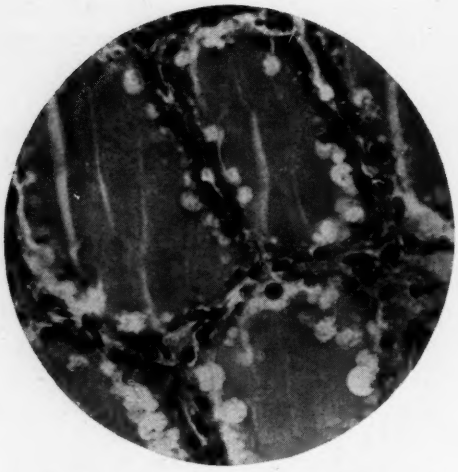


FIG. 93.—Simultaneous tracheostenosis and subtotal thyroidectomy. Neck remnant (Guinea-pig 25). Same animal as *Fig.* 92 after simultaneous tracheostenosis and subtotal thyroidectomy. Acini are large. Epithelial cells are flattened. Granules are indistinct; no mitotic figures. Colloid fills the entire lumen; it is, however, vacuolated. (× 400.)

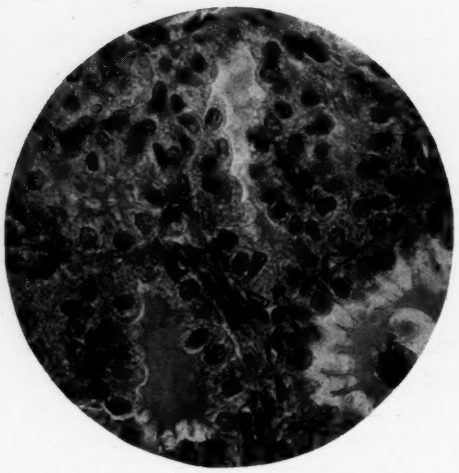


FIG. 94.—Simultaneous tracheostenosis and subtotal thyroidectomy. Neck remnant (Guinea-pig 68). Acini are irregular. Epithelial cells high and wide; granules distinct; mitotic figures present. Colloid is diminished and in some alveoli absent. Moderate grade of hypertrophy (Grade III–IV). (× 400.)

EXPERIMENT V: *The Effect of Partial Tracheostenosis on the Hypertrophic Remnants.*—Six successful experiments were carried out. One and one-half to one and three-quarter lobes of the thyroid were removed; these served as histological controls. After fifteen to twenty-one days sections were taken from the remnant and partial tracheostenosis was instituted. These sections showed varying

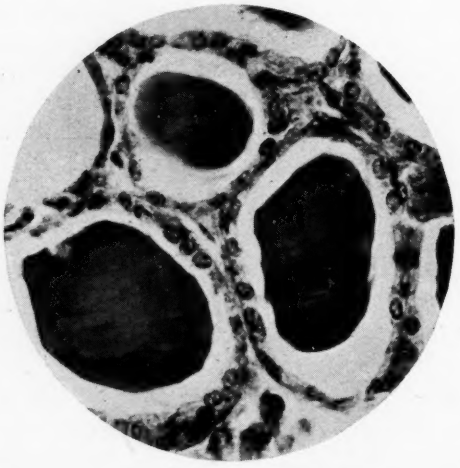


FIG. 95.—Effect of partial tracheostenosis on the hypertrophic neck remnant (Guinea-pig 52). Normal thyroid (control). (× 400.)

degrees of hypertrophy from a trace (Grade IV–V) to the highest degree (Grade I). Nine to thirteen days following tracheostenosis the animals were sacrificed; all showed occlusion of the trachea to approximately one-quarter of its normal diameter. The thyroid gland remnants were sectioned. In three animals varying degrees of

reversion to the colloidal phase were observed (*Figs.* 95–97); in the other three hypertrophic changes had persisted. After the first operation there was little

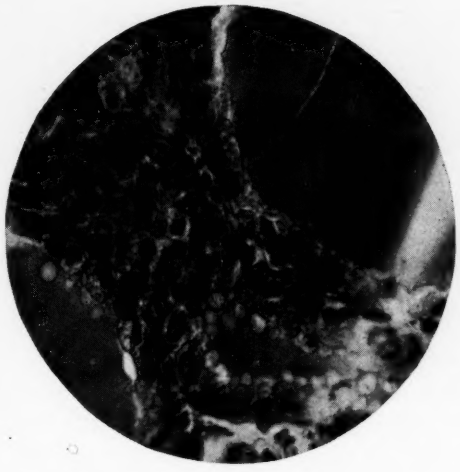


FIG. 96.—Effect of partial tracheostenosis on the hypertrophic neck remnant (Guinea-pig 52). Some of the alveoli are wide; others are irregular. Epithelial cells are higher than the normal. In some they are high and wide; granules distinct. Colloid diminished in some of the alveoli; in others it fills the lumen. Very moderate hypertrophy. (Grade IV). (× 400.)

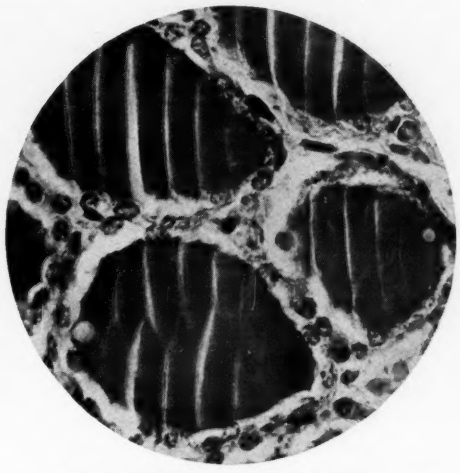


FIG. 97.—Effect of partial tracheostenosis on the hypertrophic neck remnant (Guinea-pig 52). Acini are larger than the normal. Epithelial cells are flattened. Granules indistinct; no mitotic figures. Colloid is solid and fills the entire lumen. There has been a reversion to the colloidal phase. Compare this with *Fig.* 96. (× 400.)

change in weight, except one which gained 133 grm. After the second operation all showed a small loss of weight, except one which gained 45 grm.

EXPERIMENT VI: *The Effect of Partial Tracheostenosis on Compensatory Hypertrophy of Thyroid Remnants and Autotransplants.*—In seven successful experiments

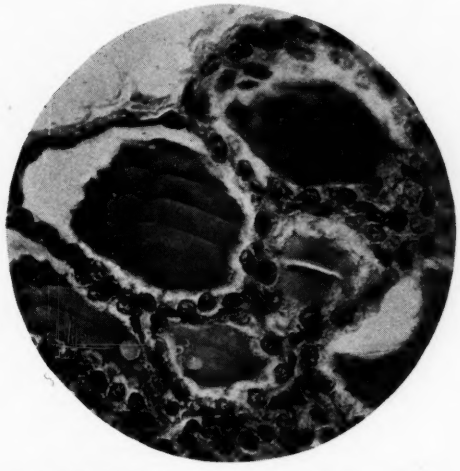


FIG. 98.—The effect of partial tracheostenosis on compensatory hypertrophy of thyroid remnants and autotransplants (Guinea-pig 72). Normal thyroid (control). (× 400.)

one and three-quarter lobes of the thyroid gland were excised. One lobe was transplanted into the subcutaneous tissue of the abdominal wall; the remaining

portion served as a histological control (*Fig.* 98). After fifteen to twenty-one days sections were made from the thyroid remnant of the neck (*Fig.* 99) and of the

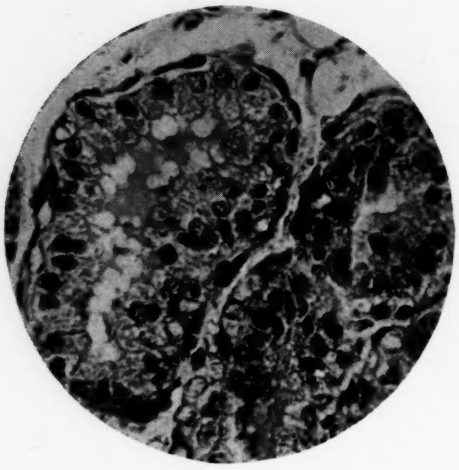


FIG. 99.—The effect of partial tracheostenosis on compensatory hypertrophy of thyroid remnants and autotransplants: neck remnant (Guinea-pig 72). Alveoli are irregular. Epithelial cells are high and wide. Granules distinct. A mitotic figure is seen in this plate. Colloid is markedly diminished, adherent, and vacuolated. Decided hypertrophy (Grade III). (× 400.)

FIG. 100.—The effect of partial tracheostenosis on compensatory hypertrophy of thyroid remnants and autotransplants: autotransplant (Guinea-pig 72). Similar picture to that seen in the neck remnant (*Fig.* 99). Decided hypertrophy (Grade III). (× 400.)

FIG. 101.—The effect of partial tracheostenosis on compensatory hypertrophy of thyroid remnants and autotransplants: neck remnant (Guinea-pig 72). The alveoli are large; epithelial cells are flattened; a few are of cuboidal type. Granules indistinct. Colloid fills the entire lumen. This represents a reversion to the colloidal phase. Compare *Fig.* 99. (× 400.)

FIG. 102.—The effect of partial tracheostenosis on compensatory hypertrophy of thyroid remnants and autotransplants: autotransplant (Guinea-pig 72). Alveoli are large and regular. Epithelial cells are of the cuboidal type. Colloid fills the entire lumen. Reversion to the colloidal phase. Compare *Fig.* 100. (× 400.)

autotransplant (*Fig.* 100). These sections showed varying degrees of hypertrophy, from very moderate (Grade IV) to marked (Grade II). The animals showed no

marked change in weight. At this time partial tracheostenosis was instituted, and after ten to twelve days the animals were sacrificed. In each animal the trachea was occluded to about one-quarter of its normal diameter. Four of the animals showed almost no loss of weight; two a loss of 88 and 107 grm.; while one gained 54 grm. Sections were taken from the neck remnants and from the autotransplants (*Figs.* 101, 102). There was a definite reversion to the colloidal phase in both neck remnants and autotransplants in three of the animals. Of the other four, in one there was definite reversion in the autotransplants but only slight changes in the neck remnant; in another there was slight reversion to the colloidal phase in the autotransplant with definite reversion in the neck remnant; the changes in the other two were very slight or absent altogether.

DISCUSSION

These experiments have confirmed previous reports that after excision of one and three-quarter lobes of the thyroid, the remnant showed definite hyperplasia, and, further, that identical changes occurred in autotransplants when one of the excised lobes was transplanted.

It has also been confirmed that when the trachea is occluded to about one-quarter of its diameter an opposite change resulted, the colloid, or resting phase, being produced.

When both these procedures were carried out simultaneously the colloid phase predominated in some experiments, while hyperplasia occurred in others, the final histological picture apparently depending on which factor predominated.

It was thus possible by these simple surgical means to produce either hypertrophic or hypotrophic gland changes at will. The hyperplasia produced by subtotal resection is generally considered to be compensatory in character. The remnant left by excision hypertrophies to take on the work of the whole gland in order to supply the need for the body for thyroid secretion.

Breitner presumed that the colloid phase which followed partial tracheostenosis was due to a decreased oxygen intake, leaving less oxygen available for tissue oxidation, and thus a lowered metabolic rate. There was thus a lessened demand for thyroid secretion, resulting in the gland changing over to the hypoactive or colloid phase. Though metabolic rates have not been determined, this would appear a reasonable explanation, and, so far as is known, no experimental evidence has been brought to disprove Breitner's assumption. Consequently it is suggested that the thyroid gland changes histologically to hyperactive or hyperplastic type in response to increased body demand, and to the colloid or hypoactive phase when the demand is lessened.

A series of experiments were now undertaken to demonstrate whether or not the introduction of tracheostenosis would change a hypertrophic remnant to a colloidal type of gland. Hypertrophy was first produced by means of subtotal excision and confirmed histologically. Tracheostenosis was then instituted. When the animals were later sacrificed three of the six thyroid remnants showed definite reversion to the colloidal phase. The animals were healthy at death, none showing any great loss of weight; in fact, one showed a gain of 43 grm.

Similar changes from hyperplasia to the resting phase were next produced in autotransplants. This ruled out the possibility of the changes being due to

mechanical factors at the site of operation or to the influence of a nervous mechanism. The changes were evidently due to a blood-borne factor. In this set of experiments, in three animals there was definite reversion to the colloid phase in both remnant and autotransplants; in another the transition was marked in the remnant, but only slight changes occurred in the transplant; the opposite result was noted in the fifth animal, where the change was marked in the transplant but only showed up very slightly in the remnant; in the other two animals in this series only very slight, or negligible, changes occurred in both remnants and transplants.

Several variable factors have thus been shown to play a definite part in thyroid function. The importance of iodine, the most active constituent of thyroxine, has been shown repeatedly (Kendall, Lenhart, Loeb, Marine, et al.). Clinically the cellular, hyperplastic gland seen in Graves' disease changes to a colloid type when iodine is administered. Also, with regulation of iodine intake in hilly districts, colloid goitres have been greatly diminished in frequency.

A review of Collip's work, together with that of several other investigators who have produced thyroid changes by means of extracts of the anterior pituitary, demonstrates that antagonistic hormones are present in the blood which definitely regulate the activity of the thyroid gland, the thyreotropic hormone increasing it, whilst the antithyreotropic hormone decreases it. These changes are accompanied for the most part by changes in the thyroid to a hyperplastic or colloid type respectively.

We have endeavoured to show that these identical changes can be produced by increasing or decreasing the body demands on the thyroid. With a relatively increased demand, as produced by subtotal thyroidectomy, hyperplasia occurs; with a decreased demand, as produced by partial tracheostenosis, hypoplasia, or a colloid gland, is produced. It is therefore evident that in the normal control of thyroid function several factors play a part. Resulting from a change in body requirements at one end, definite changes occur in the gland at the other. That this occurs under normal physiological control is well recognized. Loeb observed differences in the degree of change during winter and during summer. During the growth period, menstruation, and pregnancy, the thyroid becomes more active owing to increased body requirements. These changes would appear to be under definite control of the finely balanced antagonistic thyreotropic and antithyreotropic hormones as demonstrated by Collip. The thyreotropic hormone originates in the anterior lobe of the pituitary; where the antithyreotropic hormone, which Collip has isolated from the blood serum, originates is not yet known. The stimulus leading to the production of these hormones, when body requirement is changed, may be transmitted through the autonomic nervous system.

As a result of an upset in the relationship between the thyreotropic and antithyreotropic hormones the thyroid is immediately affected, either becoming more active or less so. Since organic iodine, the most important constituent of thyroxine (Kendall), is lessened in the active gland and increased in the blood, as shown by Loeb, it is evident that the organic blood iodine must be affected during these changes. Whether the antagonistic thyreotropic and antithyreotropic hormones control the thyroid gland through the mobilization or immobilization of iodine is not known. Since the function of the thyroid is to produce thyroxine, it is more likely that the thyroid cells themselves have the specific property of controlling

the organic blood iodine and they in turn are under the governing influence of the thyreotropic and antithyreotropic hormones. Be that as it may, the following sequence of events appears likely to us. Since the demand for thyroxine becomes acute after subtotal thyroidectomy, there is an increase of thyreotropic hormone with resultant hypertropic changes in the gland and increased circulating thyroxine. Further, it is known that after six to eight weeks the compensatory hypertrophic gland reverts to the normal; now the antithyreotropic substance is increased with a diminution of thyroxine secretion as the body requirements are being met. During tracheostenosis there is a lessened demand for thyroxine which is reflected in an increase of antithyreotropic substance with lessened circulating thyroxine and consequent iodine storage. Similarly when tracheostenosis causes the compensatory hypertrophic gland to revert to the colloid phase there is an upset in thyreotropic and antithyreotropic hormones as a consequence of altered metabolic requirements. That there may be a hormone regulation in all these processes becomes apparent since we have demonstrated identical changes in autotransplants The chain of interrelationship between body requirements, antagonistic thyreotropic and antithyreotropic hormones, and iodine in physiologic thyroid control would appear to be established; for all three factors, under certain conditions, can produce identical changes in the histological picture of the thyroid.

SUMMARY

1. Extirpation of one and one-half to one and three-quarter lobes of the thyroid gland resulted in varying degrees of hypertrophy of the remnant, from a trace to marked hypertrophy.

2. Similar degrees of hypertrophy in autotransplants were noted.

3. Partial tracheostenosis of the trachea induced in guinea-pigs a colloid phase of the thyroid.

4. Removal of one and three-quarter lobes of the thyroid gland and simultaneous partial tracheal occlusion induced a colloid phase of the thyroid.

5. Reversion from the hypertrophic phase to the colloid phase of the thyroid gland occurred in neck remnants alone and simultaneously in both neck remnants and autotransplants.

6. These changes in thyroid histology are due to a blood-borne factor.

7. The close interrelationship between body requirements for thyroxin, thyreotropic and antithyreotropic hormones, and iodine has been established.

The authors wish to express their indebtedness to Professor Edward Archibald, Professor J. C. Simpson, and Dr. D. J. Bowie for many helpful suggestions and for the preparation of histological sections.

REFERENCES

[1] LOEB, LEO, *Jour. Med. Research*, 1919, xl, 199.
[2] LOEB, LEO, and HESSELBERG, CORA, *Ibid.*, 265.
[3] LOEB, LEO, and HESSELBERG, CORA, *Ibid.*, 1920, xli, 283.
[4] LOEB, LEO, *Ibid.*, 481.
[5] LOEB, LEO, and KAPLAN, E. E., *Ibid.*, 1924, xliv, 557.
[6] LOEB, LEO, *Amer. Jour. Pathol.*, 1926, ii, 19.

[7] LOEB, LEO, *Ibid.*, 1929, v, 71.
[8] LOEB, LEO, *Ibid.*, 79.
[9] LOEB, LEO, and BASSETT, R. B., *Proc. Soc. Exper. Biol. and Med.*, 1929, xxvi, 860.
[10] CRISTIANI, H., *Comptes rend. Soc. de Biol.*, 1903, iv, 782.
[11] CRISTIANI, H., and CRISTIANI, Mme A., *Rep. Internat. Conf. Goiter*, 1927, 97. Berne : 1929.
[12] REICH, A., and BLAUEL, M., *Beitr. z. klin. Chir.*, 1912–13, lxxxii, 475.
[13] BREITNER, B., *Acta chir. Scand.*, 1924, lvii.
[14] BREITNER, B., *Beitr. z. klin. Chir.*, 1925, cxxxiv, 380.
[15] CARRARI, G., *Arch. ital. de Otol.*, 1931, xlii, 224.
[16] ABBOTT, A. C., GOODWIN, A. M., and MELTZER, S., *Canad. Med. Assoc. Jour.*, 1933, xxviii, 5, 481.
[17] ANDERSON, E. M., *Ibid.*, 23.
[18] KROGH, M., LINDBERG, A. L., and OKKELS, H., *Acta Pathol. et Microbiol. Scand.*, 1932, ix, 37.
[19] BAUMANN, E. J., and MARINE, D., *Proc. Soc. Exper. Biol. and Med.*, 1932, xxix, 1220.
[20] ANDERSON, E. M., and COLLIP, J. B., *Ibid.*, 1933, xxx, 680.
[21] ANDERSON, E. M., and COLLIP, J. B., *Jour. of Physiol.*, 1934, lxxxii, 11.
[22] COLLIP, J. B., and ANDERSON, E. N., *Lancet*, 1934, i, 76.
[23] COLLIP, J. B., "Wm. Henry Welch Lectures", *Mt. Sinai Hospital*, 1934, i, 28.
[24] ANDERSON, E. M., and COLLIP, J. B., *Lancet*, 1934, i, 784.
[25] CLOSS, K., LOEB, L., and MACKAY, E. M., *Jour. Biol. Chem.*, 1932, xcvi, 585.

CHOLECYSTOGRAPHY: ITS PRESENT CLINICAL VALUE

By ROBERT McWHIRTER

CHIEF ASSISTANT, X-RAY DEPARTMENT, ST. BARTHOLOMEW'S HOSPITAL

THE object of this investigation was to attempt to find out the most reliable technique for cholecystography and to check the significance of various conclusions which have been based on the X-ray examination of the gall-bladder following the administration of sodium tetraiodophenolphthalein. The volume of material was relatively enormous, and accordingly it was hoped that the relative proportions of various pathological conditions would be more accurate than would have been the case if the investigation had been undertaken on a smaller number of cases. At the Mayo Clinic some five thousand gall-bladders are examined each year by the Graham dye test, and a large proportion are checked by operation, which can be the only profitable method of ascertaining the accuracy of the reports issued. It is interesting to observe, too, that all X-ray reports are based entirely on the films, the radiologist having no knowledge of the clinical condition of the patient except in those cases which have had previous operation on the gall-bladder. Following surgical intervention the operative findings and histological investigations are conveyed to the X-ray Department, and indeed it is not infrequent for a member of the X-ray staff to be actually present at the operation. By such careful co-operation between the surgeon and the radiologist an extraordinarily high degree of accuracy has been obtained.

The following points are considered in this paper: (*I*) *The roentgenological reporting of cholecystograms;* (*II*) *The technique of administration of the dye;* (*III*) *The analysis of the cholecystographic data for* 1932 *at the Mayo Clinic;* (*IV*) *The basis on which the diagnosis of tumours of the gall-bladder can be made;* (*V*) *Duodenal and gastric ulcer as a cause of non-filling of the gall-bladder;* (*VI*) *Disease of the liver as a cause of non-filling;* (*VII*) *The significance of delayed emptying;* (*VIII*) *The significance of calcium deposit in the gall-bladder;* (*IX*) *The frequency of carcinoma in cases with gall-stones.*

I. THE ROENTGENOLOGICAL REPORTING OF CHOLECYSTOGRAMS

In order to obtain a good cholecystogram, Barclay[1] has pointed out the conditions which must be present: (1) The salt must circulate in the blood in sufficient quantity; (2) The liver must be functioning actively and excreting the salt; (3) The mucous membrane of the gall-bladder must be sufficiently healthy to concentrate its contents.

In 1927 Caylor and Bollman[2] examined the relationship between the bilirubin content of gall-bladder bile and certain pathological conditions of the gall-bladder. The bilirubin content, determined by the van den Bergh method, of 105 gall-bladders removed at operation was compared with the pathological findings. From

this study they concluded that, in the majority of cases, the more disease there is present in the gall-bladder the lower is its bilirubin content. The important exception to this general rule is the gall-bladder with papillomata and associated hypertrophic rugæ; the significance of this finding will be discussed later.

From the above statement it might be considered that the density of the cholecystogram, which like the bilirubin content depends on the degree of concentration of the bile, would be an indication of the extent of pathological change. In fact this method of estimating the amount of pathological change in the gall-bladder has been, and is still being, used in many X-ray departments, but so many disturbing factors have to be considered that from a practical point of view it cannot be used. For instance, the weight of the patient, the amount of absorption from the bowel (in the oral method), the presence or absence of sickness and diarrhœa, the size of the gall-bladder shadow (the larger the gall-bladder is, the less dense the shadow ought to be), the possibility of the fact that the gall-bladder has already commenced to empty or has not yet reached its maximum degree of concentration, would all require to be taken into consideration.

At the Mayo Clinic the following roentgenological reports are issued: (1) Normally functioning gall-bladder; (2) Normally functioning gall-bladder with stones; (3) Normally functioning gall-bladder with tumour; (4) Poorly functioning gall-bladder; (5) Poorly functioning gall-bladder with stones; (6) Non-functioning gall-bladder; (7) Non-functioning gall-bladder with stones.

The diagnosis of poorly functioning gall-bladder is made when the shadow of the gall-bladder as given by the dye is only just visible and where its density is less than that cast by the liver or kidney. This makes allowance for the variation in thickness of the patient, which has a very definite bearing on the density of the gall-bladder in the X-ray film.

The diagnosis of non-functioning gall-bladder indicates that the gall-bladder shadow is not visible at all or that the shadow is a primary one and has not increased in density by the administration of the dye.

Unless some such method is adopted the dividing line between normally functioning and poorly functioning gall-bladders becomes a very variable one, and at present it is almost impossible to compare the results obtained at different clinics.

The diagnosis of adhesions of the gall-bladder is frequently made, but Kirklin[3] has concluded from long experience that apparent deformity of contour is rarely a safe basis of diagnosis of disease. *Figs.* 103–106 support this view, and indicate that a gall-bladder may be markedly deformed merely by extrinsic pressure from the bowel, or depend on anatomical deformity.

When a cholecystogram is constantly of hour-glass shape it indicates anatomical deformity, as no disease in the wall can be found to account for this when the gall-bladder is examined histologically. *Figs.* 107 and 108 show gall-bladders which maintained their hour-glass shape throughout the period of investigation and were considered examples of anatomical deformity. Apparent hour-glass deformity may, of course, be due to extrinsic pressure from without, the most important cause being gas in the bowel.

In cases of previous cholecystostomy the fundus of the gall-bladder is often blurred and indistinct, and an example of this is given in *Fig.* 109. It is worthy of note at this point that the gall-bladder in men of sthenic build usually lies horizontally with the fundus to the right (*Fig.* 110).

FIG. 103.—Apparent cutting off of lower end of gall-bladder. The next film showed a normal gall-bladder.

FIG. 104.—Deformity of medial side of gall-bladder shadow produced probably by the duodenal cap.

FIG. 105.—Marked deformity. Gall-bladder normal at operation.

FIG. 106.—Apparent example of bifid fundus—the next photograph showed that the outline was normal.

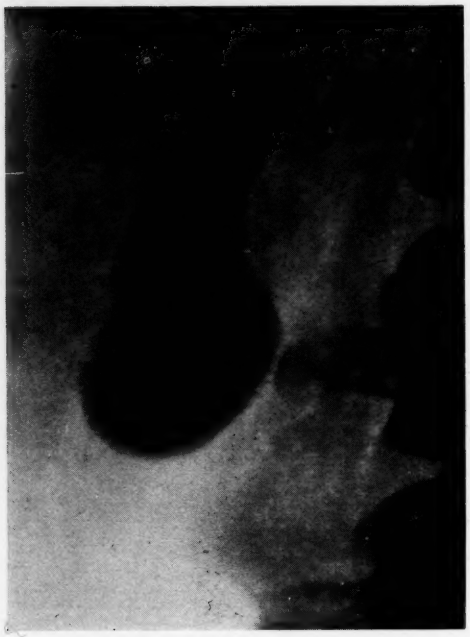


FIG. 107.—Hour-glass deformity due to anatomical causes.

FIG. 108.—Double hour-glass deformity also due to anatomical causes.

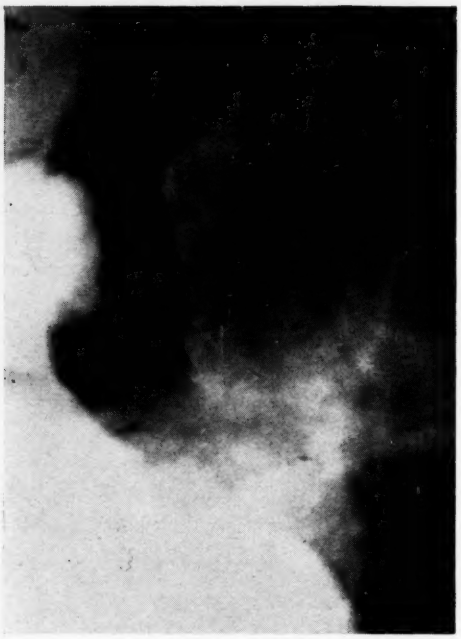


FIG. 109.—Note blurring of fundus: this patient had a cholecystostomy in 1909

Perhaps it would be interesting to state here that in addition to the diagnosis of adhesions of the gall-bladder in cholecystograms not being made, the diagnosis of adhesions to the duodenal cap is also not made at the Mayo Clinic. That such a condition exists is not disputed, and Rowden[1] has described the 'dunce's cap deformity' of the duodenum, which suggests adhesions to the gall-bladder. Thousands of duodenal caps are examined in the Mayo Clinic each year and an accuracy in the diagnosis of duodenal ulcer of over 98 per cent has been obtained —that is to say, 98 per cent of all persistently deformed duodenal caps have been proved by operation to be due to duodenal ulcer. Of the small proportion remaining (less than 2 per cent) the commonest cause was certainly gall-bladder adhesions, but since no important difference could be detected between those two types of

FIG. 110.—Example of gall-bladder in a patient of sthenic build. Note the viscus lies almost horizontally.

deformity the diagnosis of adhesions was abandoned. Attempts to arrive at this conclusion only increased the percentage of errors instead of diminishing them. Accordingly all persistently deformed duodenal caps are considered to be due to ulcer. When considered from the cholecystographic aspect very markedly deformed shadows have been found repeatedly at operation to be associated with a perfectly normal viscus. On the other hand, when adhesions are present the gall-bladder outline may be quite normal. Kirklin,[4] on examining 204 gall-bladders which appeared normal from an X-ray point of view, found that no fewer than 40 cases at the time of operation were associated with adhesions. From the above considerations it follows that even combined gall-bladder and barium meal investigation has been considered to be of little value in arriving at a diagnosis of adhesions between the gall-bladder and the duodenal cap.

II. TECHNIQUE OF ADMINISTRATION OF THE DYE

There are two main methods of giving the dye: (1) The intravenous; (2) The oral. Considerable controversy has arisen concerning which of the two methods is the better, and the dispute is not yet settled. At the Mayo Clinic the oral method

is the only one employed, and I hope to show that the results so obtained are of such a high order of accuracy that they at least equal those obtained by the intravenous method. But the oral technique is often faulty, and in order to obtain good results certain important points must be carefully observed. Kirklin[3] insists on the following points :—

1. The dye must be given in sufficient quantity. He recommends 4 grm. as the standard dose for all adult patients regardless of their weight. A reduction is only made in the case of children under fifteen or sixteen years of age.

2. The dye must be given in a readily absorbable form. The use of capsules, etc., has not been found to be necessary, and the capsules may not be absorbed and the dye remain enclosed.

3. The dye must be given in such a manner that it will not produce undue nausea and vomiting. Many persons can take the dye in simple aqueous solution, but some become nauseated or object to the taste. If there is doubt, 2 to 3 gr. of luminal one hour before the meal will prevent sickness and in addition will tend to check diarrhœa. Between four and six thousand cholecystograms are made in the Mayo Clinic each year and experience has shown that those two objections are in the main surmounted by giving the dye in a glassful of fruit-juice or carbonated water. Grape-juice is preferred. The frequent practice of giving the dye on an empty stomach has been abandoned, and it has been found best to give the dye immediately after a full meal, and this meal should contain a minimum of fat.

4. The dye must be given under conditions that will not hamper its evacuation from the stomach, its absorption from the bowel, or its accumulation and concentration in a normal gall-bladder. If a fatty meal is given with the idea of emptying the gall-bladder of the bile it already contains, the error in diagnosis is increased because fat greatly delays evacuation from the stomach. Levyn[5] observed that when a fatty meal immediately preceded barium examination there was almost invariably a six hours' gastric residue. Consequently there will be delay in evacuation of the dye from the stomach, and the prolonged flow of fatty foods through the duodenum will interfere with concentration in the gall-bladder. Delarie,[6] too, has shown that in animals fat renders a greater amount of the dye in the small bowel insoluble.

Absorption from the bowel is interfered with by giving purgatives, and enemata on the morning of the examination have been found satisfactory in emptying the colon. Objections have been raised to the administration of an enema because, it is alleged, one cannot tell how much dye has remained unabsorbed in the colon. Obviously this is of no importance, for if the gall-bladder is healthy it will have absorbed as much dye as it can, and if on the other hand it is pathological it will not absorb any, and in either case only the unabsorbed dye will be seen in the colon. However, an enema is not always necessary, and its administration can be conveniently postponed till after the first film.

This method, employing the above essential principles, has been in use at the Mayo Clinic for more than three years. The details of the examination are as follows :—

The patient receives 4 grm. of sodium tetraiodophenolphthalein (the pure drug is used) dissolved in 30 c.c. of distilled water and is given the following printed instructions :—

a. At 6 or 7 p.m. eat supper of the usual amount, but without cream, eggs, butter, or other fats.

b. Immediately after supper empty the entire contents of this bottle (the dye) into a glassful of grape-juice, stir well, and drink all.

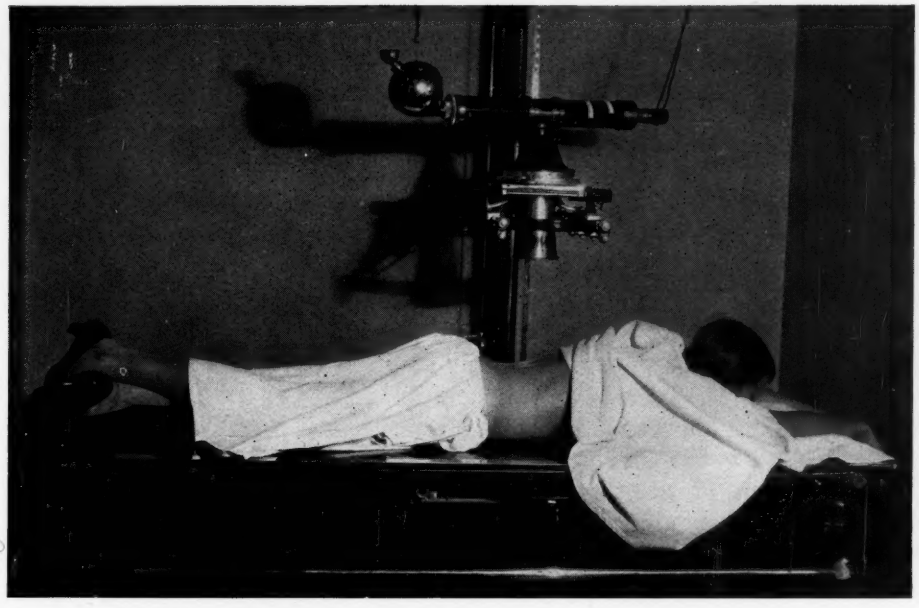


FIG. 111.—Position normally assumed by patient on table. Note uncomfortable attitude and incomplete relaxation of muscles.

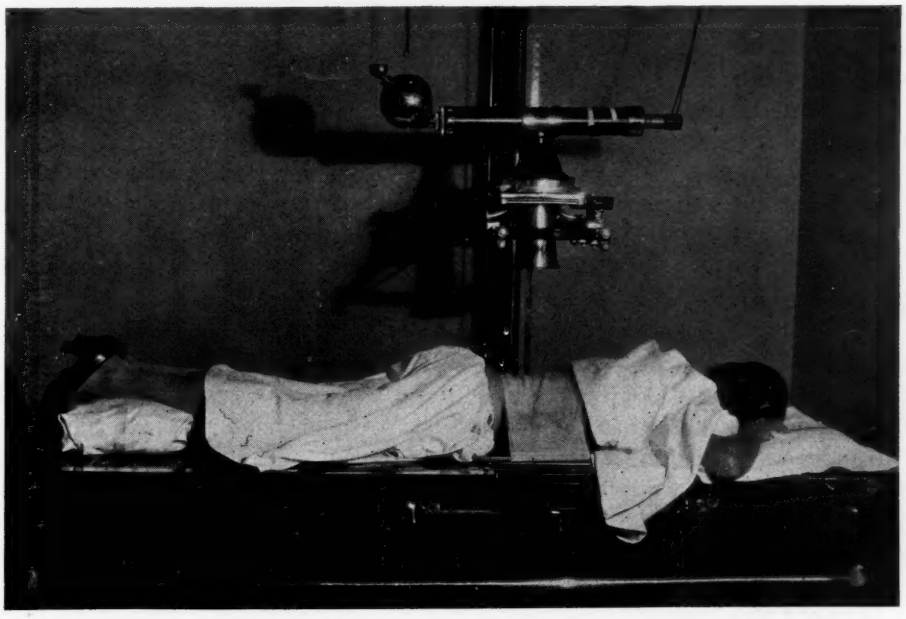


FIG. 112.—Position in which patient should be placed. Note comfortable position of head and arms, and pillow under ankles. The canvas band aids in immobilization.

c. Do not take a laxative or any other medicine.

d. At 7 o'clock next morning take a rectal injection of warm salt solution until the water returns clear.

e. Do not eat breakfast; you may drink water, black coffee, or clear tea.

Films (anterior views only) are taken at the fourteenth and sixteenth hours after the dye and again at the twentieth hour, the patient having partaken of lunch with a glassful of cream and milk in equal parts three-quarters of an hour prior to this last examination.

At the time of examination it is essential in order to avoid movement that the patient be placed comfortably on the X-ray table, which is equipped with a flat Potter-Bucky grid. He lies with his cheek to the pillow, his arms forward, and his ankles supported by a cushion. To secure thorough immobilization a broad canvas band is drawn tightly over the back (*Figs.* 111, 112). The picture is taken in expiration, and the exposure should not exceed one-half to one second, so as to avoid movement of either the patient or the gall-bladder by peristaltic movements of the bowel. *Figs.* 113–115 show how the shadows of gall-stones can be completely obliterated by slight movement. Recently at St. Bartholomew's Hospital films in the erect posture have been taken routinely in addition to prone films. So far no advantage has been obtained. It has been stated that it is possible to observe small stones which fall to the fundus and which would not have been visible otherwise. But it would seem unnecessary to do this, for with careful technique and the aid of the fatty meal very tiny stones can be detected (*see Fig.* 138). Moreover, it is more difficult for the patient to keep steady in this position. It may, however, be of value in differentiating between a stone and a tumour.

The first roentgenogram is inspected for errors of technique, and if the gall-bladder is obscured by gas, the technician massages the abdomen to displace the gas or requires the patient to repeat the enema. If the shadow is obscured by the ribs, subsequent films are taken in inspiration and the tube may be decentred to throw the gall-bladder clear of the spine. *Figs.* 116 and 117 show how the gall-bladder may be separated from the colon shadow by suitable compression.

As already mentioned, it is very difficult to compare the results obtained at different clinics because of the variation in the definition of the terms 'normally' and 'poorly-functioning' gall-bladder. The intravenous method, employed by Graham,[7] has given excellent results, but when compared with the results obtained by Kirklin[3] they cannot be said to be better. In order, however, to be able to make a fair comparison between the two methods it is essential to compare the accuracy obtained in the same clinic where the two methods have been used.

Some time ago Kirklin[3] checked a series of cases of non-filling of the gall-bladder when the oral method had been used, by intravenous injection of the dye, and found the increase in filling was about 1 per cent. In addition he showed that if the cases of non-filling had the oral method repeated, the increase of filling of the gall-bladder was 1 per cent. Consequently it would appear that the oral method as employed by Kirklin will give a cholecystogram in as many cases as the intravenous, if those cases which do not fill on the first examination have the oral method repeated. It is the practice at the Mayo Clinic to repeat the oral administration of the dye in twenty-four hours if no shadow is obtained at the first examination.

Hawley[8] also compared the results obtained in 265 cases examined by the oral technique with 235 cases in which the intravenous method was used. The cases

FIG. 113.—Note shadow of large gall-stone.

FIG. 114.—Same patient as shown in *Fig.* 113 : no gall-stone is visible now ; patient has moved slightly.

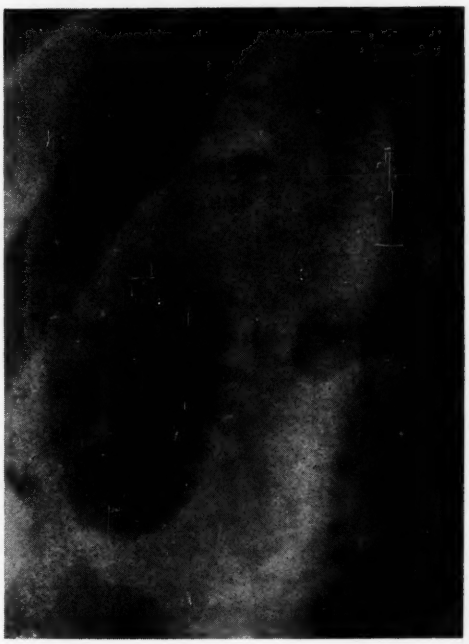


FIG. 115.—Film where the stones could easily be missed by movement.

were selected at random. It is important to realize, however, that his method of oral administration varied somewhat from that of Kirklin. Nevertheless, and in spite of the fact that he began the investigation with the idea that the intravenous method was superior, he concluded that the oral method was as accurate as the intravenous, and finally adopted the former as his method of investigation for future

FIG. 116.—Gall-bladder hidden by colon. No stones visible.

FIG. 117.—Same case as *Fig.* 116 : stones now visible. This film was taken after a compression band had been drawn tightly over the lower ribs. An alternative method would have been to administer an enema.

cases. (The proved errors were 9 per cent in the intravenous and 10 per cent in the oral method.)

Certainly the intravenous route of administration is now almost entirely free from serious complications, but if any of the dye is accidentally injected into the tissues around the vein, necrosis and sloughing of the subcutaneous tissues may result, with great dealy in healing. Intravenous injection can often be tedious and troublesome, and in difficult cases may necessitate cutting down on the vein.

The whole process is naturally a greater ordeal to the patient than the oral method, and if results can be obtained by the latter method which are as good, the oral method is certainly the one of choice.

Contra-indications to Employment of Graham Test.—Cholecystography should not be used in patients suffering from obstructive jaundice, because fatal pancreatitis has sometimes followed such cases (Choyce and Beattie[9]). In acute cases Hawley[8] concluded that the information gained is not worth the suffering because the dye upsets these patients very much. On the other hand, in cases of chronic cholecystitis Nickel and Judd[10] have shown that sodium tetraiodophenolphthalein on entering the gall-bladder has a bacteriostatic influence on the organisms it contains, so that the administration of the dye may be actually beneficial in those cases.

III. ANALYSIS OF CHOLECYSTOGRAPHIC DATA FOR 1932

During 1932 at the Mayo Clinic 4676 patients were examined by the use of cholecystography and 732 were operated on. The cholecystographic diagnosis, whether positive or negative, was confirmed in 696 out of the 732 cases (95 per cent).

CHOLECYSTGRAPHIC DATA FOR 1932

DIAGNOSIS	CASES	FINDINGS AT OPERATION								DIAGNOSIS CONFIRMED AT OPERATION
		Gall-stones	Tumours	Cholecystitis Grade				Miscellaneous	Normal	
				Not graded	2	3	4			
										Per cent
Normally functioning gall-bladder	287	4	2	19	4		1		257	89·5
Poorly functioning gall-bladder ..	39	28 (71·8%)		5		1	2	1	2	94·8
Non-functioning gall-bladder ..	106	90 (84·9%)	3	4	3		2	1	3	97·1
Normally functioning gall-bladder with stones 124	294	293	1							99·6
Poorly functioning gall-bladder with stones 78										
Non-functioning gall-bladder with stones 92										
Tumour	6		6							100·0
Total ..	732	415	12	28	7	1	5	2	262	

445 cases with positive cholecystographic data; 6 errors (98·6 per cent correct). Of 732 diagnoses, 696 (95·0 per cent) were confirmed.

415 cases with gall-stones at operation; 411 (99·0 per cent) with positive cholecystographic data. Of the 415 cases, gall-stones were visualized and reported in 294 (70·8 per cent).

470 cases with disease of the gall-bladder at operation; positive cholecystographic data in 440 (93·6 per cent).

262 cases without disease of the gall-bladder at operation; negative cholecystographic data in 257 (98·0 per cent).

Among 287 patients with normal cholecystograms who were operated on, chiefly for diseases other than that of the gall-bladder, surgical exploration confirmed the cholecystographic diagnosis in 257 (89·5 per cent). It is well known that the highest percentage of errors is caused by diseased gall-bladders which maintain their function sufficiently to produce a normal shadow. If the intravenous method gave a higher percentage of filling of the gall-bladder, the percentage of errors would be increased.

Of 445 patients with positive cholecystographic data, 439 (98·6 per cent) had gall-bladder disease. In 415, gall-stones were found at operation, and of these cases the evidence of the cholecystographic data showed a pathological condition of the gall-bladder in 411 (99 per cent), gall-stones as such being diagnosed in 294 (70·8 per cent). In 6 cases in which a diagnosis of tumour of the gall-bladder had been made the diagnosis was confirmed, but papillomas were also found in a few cases in which this specific diagnosis had not been made.

It will be seen from the table that gall-stones can be recognized in a very high percentage of cases (70·8 per cent). Moreover, their presence can be suspected in a still higher number of cases, for 71·8 per cent of the poorly-functioning and 84·9 per cent of the non-functioning gall-bladders were found to contain stones. This represents a very real contribution to diagnosis, because before the use of the dye test Pfahler[11] in 1914 gave 50 per cent as the average of cases of gall-stones in which the calculi could actually be seen on the plain film. This figure of 50 per cent is probably considerably higher than is usually stated in this country, for Choyce and Beattie[9] gave only 20 per cent, and Rowden[12] stated that not one in ten cases of stones was visible before the dye test was used. (*Figs.* 118–120.)

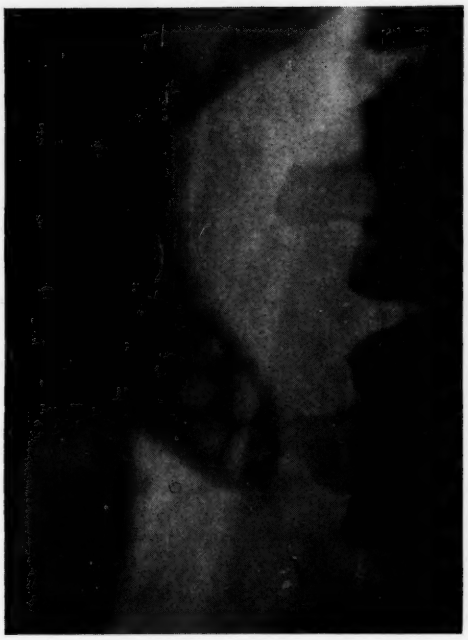
The Interpretation of the Term 'Poorly-functioning' Gall-bladder without Stones in Terms of Pathology.—A series of 45 cases checked by operation is given and was made up as follows:—

Cholecystitis with gall-stones	35
Cholecystitis	6
Cholecystitis with papilloma	2
Carcinoma of pancreas	1
Gall-bladder normal	1

The Interpretation of the Term 'Non-functioning' Gall-bladder without Stones in Terms of Pathology.—In this group a series of 112 cases checked by operation are considered:—

Cholecystitis with gall-stones	95
Cholecystitis	7
Carcinoma of the gall-bladder	1
Carcinoma of ampulla of Vater	1
Carcinoma of ducts with stones in gall-bladder	1
Fistula of the gall-bladder	1
Stones in the common bile-duct only	1
Cholangitis	1
Congenital absence of the gall-bladder	1
Carcinoma of pancreas	1
Gall-bladder normal	2

It will be readily observed from the above tables that by far the commonest cause of poorly-functioning and non-functioning gall-bladders is cholecystitis with gall-stones. It will also be noted that two cases of carcinoma of the pancreas are included in those tables. This is interesting, especially when the case of stone



FIGS. 118, 119.—Radiotranslucent stones, or ' negative shadows ', which would not be visible without dye.

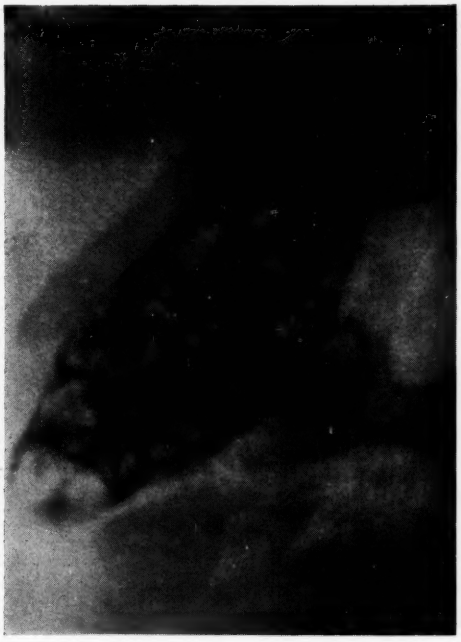


FIG. 120.—An enormous number of radiotranslucent stones. Generally in such a case no contrast filling is obtained and the gall-bladder falls into the non-functioning group.

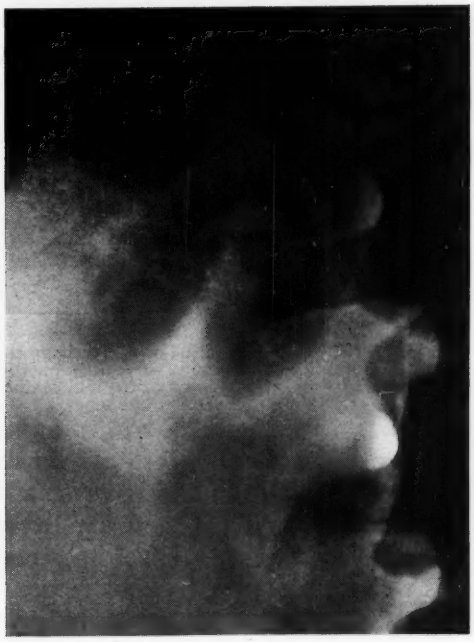


FIG. 121.—Double gall-bladder.
(*By courtesy of Dr. E. W. Twining.*)

in the common bile-duct is also considered, for it would appear that obstruction to the outflow of bile interferes with the production of a shadow. Probably the increased pressure so damages the liver that it ceases to function, for it is a well-known surgical finding in cases of long-standing obstruction that the biliary system is filled with clear fluid and not with bile. This so-called ' white bile 'may indeed be the only part of the body which is not stained yellow. The explanation of the phenomenon lies in the fact that the bile is absorbed from the gall-baldder and ducts and the pressure is too high for the liver cells to function. But the glands lining the common bile-duct can secrete this clear fluid under a slightly higher pressure and so the duct system becomes filled with their secretion. In view of this occurrence, then, non-filling of the gall-bladder with dye is what one would expect.

Congenital absence of the gall-bladder of course is rare. One case exists in the London Hospital Museum. Another example of congenital abnormality is duplication (*Fig.* 121), which may be complete, as in the case reported by Sherren,[13] or the gall-bladder may have merely a bifid fundus. Congenital absence of the bile-ducts is not a radiological problem for the child dies soon after birth. Fistula of the gall-bladder will obviously prevent formation of a shadow.

FIG. 122.—Opaque material in bowel superimposed on faint gall-bladder shadow. A subsequent photograph showed material to the left of the middle line and apparently in the transverse colon.

Examples of Possible Errors in Diagnosis.—

1. Calcification of the rib cartilage. Doubt is easily removed if pictures are taken in inspiration and expiration, and it will then be seen that the calcified area does not move with the gall-bladder shadow.

2. Opaque material in bowel. This type of shadow will vary in position in the different films and may be absent in one or two of the films (*Fig.* 122). Opaque material in diverticula of the transverse colon has been considered as a possible source of error in diagnosis by Potter.[14]

3. Renal stones are easily recognized as being distinct from the gall-bladder shadow and as moving with the kidney shadow.

4. The cystic gland lying in the angle between the cystic duct and the common hepatic duct may calcify and simulate a stone, but the shadow is again apart from the gall-bladder shadow. To differentiate it from a stone in the common bile-duct it is well to remember that obstruction of the duct will almost certainly lead to the gall-bladder not filling, and should it fill at all, the shadow will be faint and of increased size. Moreover, the patient will have jaundice. In certain cases, either by the aid of the fatty meal or by the use of compression, it may be possible to demonstrate the common bile-duct. (*See Figs.* 129–131.)

5. Pancreatic calculi are very rare, only some forty cases having been described in the literature (Lindsay[15]).

6. Superficial tumours of the skin are best ruled out by inspection of the skin of the patient prior to X-ray examination.

7. Calcification of the right adrenal gland should not be confused with calcification of the gall-bladder wall or a calcified stone. Examples of this are given in an article by Camp, Ball, and Greene.[16]

8. Mention has already been made of the danger in drawing conclusions from distortion and irregularity of the contour.

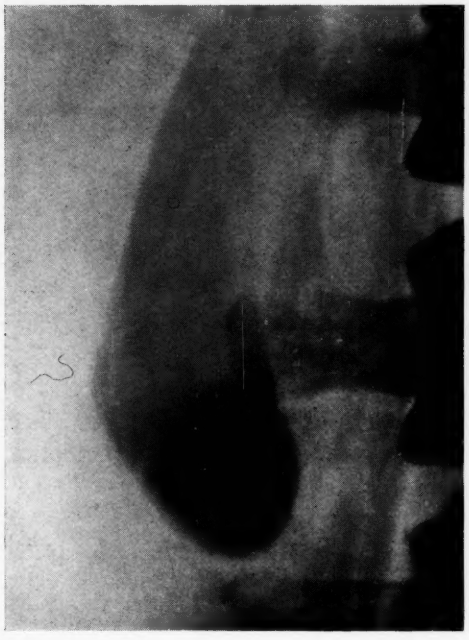


FIG. 123.—Gas in bowel superimposed on gall-bladder shadow and simulating radiotranslucent stones.

FIG. 124.—Radiotranslucent stones very similar to gas-bubbles in previous photograph.

9. Gas-bubbles in the bowel superimposed on the gall-bladder may closely simulate stone, but the diagnosis can generally be cleared up by viewing all the films and noting the variation in the shape, size, and position of the gas-bubbles. It would almost appear that the radiologist is more apt to consider a radiotranslucent stone to be a gas-bubble than vice versa (*Figs.* 123, 124).

10. The differential points between tumour of the gall-bladder and stone are given later.

IV. THE BASIS ON WHICH THE DIAGNOSIS OF TUMOUR OF THE GALL-BLADDER CAN BE MADE

Tumours of the gall-bladder were first recognized by Kirklin,[17] and their recognition was due to the careful system of checking all cases that have passed through the X-ray department—a system which unfortunately in this country is often only half-hearted.

In 1930 a small rounded radiotranslucent shadow near the fundus was interpreted as being a gall-stone, but at operation an adenoma was found. This stimulated further investigation, and now a diagnosis of tumour is frequently made at the Mayo Clinic and with an amazing degree of accuracy. Tumours as small as 1 mm. in diameter have been reported, and that this has become possible, together with the differentiation of so tiny a tumour from a stone, is a very high tribute to the excellence of the technique and the care taken in the reporting of films. But a stage further even than this high standard has now been reached, and adenoma can often be distinguished from papilloma.

Both benign and malignant tumours occur in the gall-bladder.

Benign Tumours.—The following benign tumours are described in the gall-bladder: (1) Papilloma; (2) Adenoma; (3) Fibroma; (4) Lipoma; (5) Myoma. Occasionally a piece of aberrant liver is found adhering to the wall of the gall-bladder and this may simulate a tumour. Papilloma and adenoma are the only tumours which have been detected so far by X-ray examination.

Papillomata.—Papilloma is by far the commonest simple tumour, and in 17,000 gall-bladders surgically removed at the Mayo Clinic papillomata were found in 8·5 per cent of those cases. Kaufmann[18] believes that the older a person gets, the more papillomatous the gall-bladder epithelium tends to become. These papillomata are of two types: (1) The true neoplasm; (2) The polypoid cholesterol-laden villus. The latter type is the commoner and has no tendency to become malignant. The former type when multiple, however, must be regarded as potentially malignant.

The enlarged polypoid cholesterol-laden villus is really an example of localized cholesterosis (strawberry gall-bladder). They are generally accompanied by marked hypertrophy of the epithelial lining of the gall-bladder, and Erwin and MacCarty[19] pointed out that this epithelial hyperplasia is the most striking characteristic of chronic cholecyctitis with papillomata. Caylor and Bollman[2] found that such gall-bladders gave the highest concentration of bilirubin. Stones may be present in addition and are frequently of the cholesterol variety. Boyd,[20] in fact, has suggested that a broken-off polyp may form the nucleus of a stone in strawberry gall-bladders. From the records of the Mayo Clinic the diagnosis of strawberry gall-bladder by itself would appear to be impossible.

Rossi[21] claims that strawberry gall-bladder can be identified by the following signs. The filling of the viscus is slow and emptying is always delayed. There is pain on palpation and certain 'indirect signs'. But his observations are not convincing.

The origin of the cholesterol in these villi is stated by Andrews, Schoenheimer, and Hrdina[22] to be from the blood-stream and not from the biliary cholesterol as is frequently believed. The condition then becomes comparable to xanthoma of the skin and atheroma of blood-vessels.

Papillomata generally have a diameter of less than 0·5 cm. and rarely exceed 1 cm. They are more often multiple than single.

Kirklin[17] has given the radiographic characteristics of papillomata as follows (*Figs.* 125–128):—

1. They have the same relative position even at re-examination.

2. Defects are generally clear, rounded, and small, and usually less than 0·5 cm. in diameter.

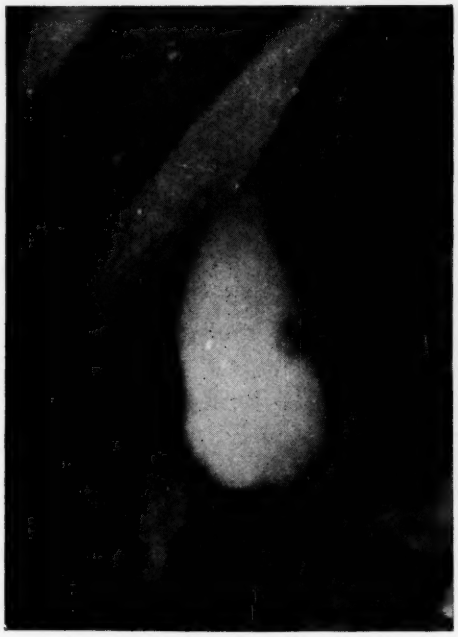


FIG. 125.—Shadow defect on medial wall of gall-bladder due to papilloma.

FIG. 126.—Photograph of this gall-bladder laid open to show papilloma.

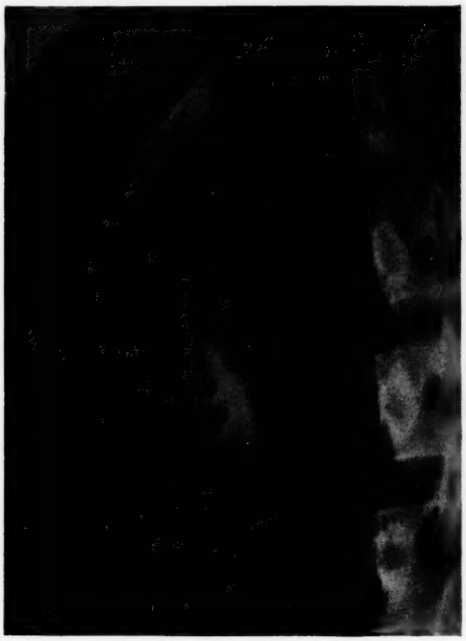


FIG. 127.—Multiple radiotranslucent areas due to papillomata fourteen hours after dye.

FIG. 128.—Same gall-bladder as *Fig.* 127 after removal, showing one large and several small papillomata.

3. They do not tend to occur immediately at the pole of the fundus and a marginal position is especially suggestive.

4. They are generally multiple.

5. When multiple the defects are well separated and never grouped closely like gall-stones.

6. They are generally most plainly visible at the twentieth hour and may only be visible at this time.

7. The cholecystogram is generally good or above average density—this is in accordance with the findings of Caylor and Bollman[2] on bilirubin content of such gall-bladders.

Adenomata (*Figs.* 129–135).—The following are the chief points in the diagnosis of adenomata :—

1. They generally occur directly at the pole of the fundus.

2. They are generally larger than papillomata. Average size 8 mm.

3. They are generally single. Of 61 cases of adenoma recorded at the Mayo Clinic between 1927 and 1931 all were single except two cases.

4. They are always sessile.

5. They are frequently associated with gall-stones ; 34 cases out of the series of 61 had gall-stones, and cholecystitis was noted in 44 cases.

6. They are seldom visible till the twentieth-hour film, although their presence may be indicated in the earlier films by a fine slit-like defect at the fundus.

In a series of 47 cases examined cholecystographically normal density was noted in 23 cases and a faint shadow was observed in a further 9 cases.

On removal of the gall-bladder they can be seen as a small button-like prominence in the region of the fundus.

Differential Diagnosis of Simple Tumours from Gall-stones.—Gall-stones are : (1) Variable in situation ; (2) Grouped closely, especially as the gall-bladder contracts ; (3) Faceted and angular ; (4) They may have a calcium coating ; (5) Even without a calcium coating they are less clearly transparent than tumours.

Malignant Tumours.—These are generally carcinomata. Sarcoma is rare. Kaufmann[18] could find only 13 cases reported in the literature.

In a series of 22,365 operations at the Mayo Clinic on the gall-bladder and biliary tract Judd and Gray[23] found primary carcinoma of the gall-bladder in 212 cases ; 74 per cent of these cases occurred in the female, so that carcinoma and gall-stones display the same sex ratio. Zenker[24] reported 72·9 per cent in females, Naunyn[25] 83 per cent, and Musser[26] 75 per cent.

The youngest patient was 23 years and the oldest 78 years, and 73·4 per cent of the cases occurred between the ages of 50 and 70 years. Stones were associated in 64·6 per cent of cases.

The carcinoma may originate at the fundus or near the cystic duct, and the gall-bladder may rapidly be filled by tumour tissue, or if the carcinoma is of the scirrhous type the walls are contracted and the lumen is obliterated. Again, when it originates near the cystic duct this becomes blocked. These factors probably in the main account for the fact that where carcinoma of the gall-bladder has been found at operation or post-mortem the X-ray report has been ' non-functioning gall-bladder '.

At the Mayo Clinic, of 16 cases examined cholecystographically 14 gave no shadow of the gall-bladder although stones were visible in 7, one case was normal

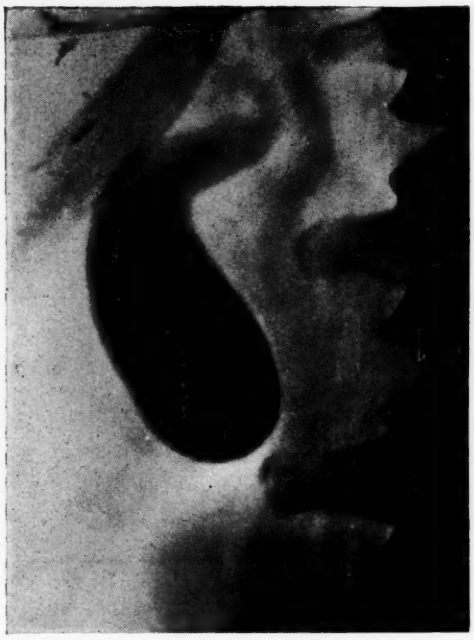


FIG. 129.—Note excellent shadow of gall-bladder. Adenoma not visible.

FIG. 130.—Same case as *Fig.* 129 twenty minutes later. Gall-bladder partially emptied. Adenoma becoming visible.

FIG. 131.—Same case as *Fig.* 129 one hour after first film. Adenoma plainly visible.

FIG. 132.—Same as *Fig.* 129, one and a half hours after first film.

This series of photographs shows the great value of the fat meal in rendering visible the tumour.

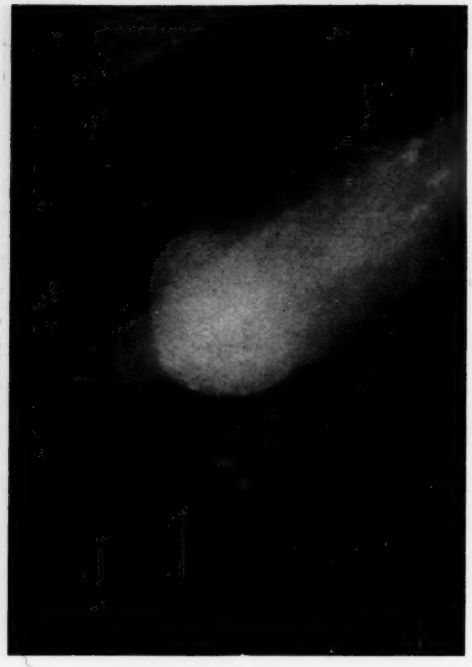


FIG. 133.—Gall-bladder lying transversely. No adenoma visible.

FIG. 134.—Same case as *Fig.* 133 after administration of fat meal. Adenoma only now visible.

FIG. 135.—Same gall-bladder as that shown in *Fig.* 134 laid open to show adenoma at fundus.

with stones, and one gave a normal shadow in which no defect could be distinguished.

Rowden[1] met with the condition only twice—in one case he detected two large stones, and in the other the gall-bladder failed to fill.

Taterka[27] reported a case with a defect in the wall which at operation proved to be a carcinoma, but apart from this one case all other attempts by cholecystography to reveal malignant tumours have failed.

Kirklin[17] has suggested that a defect which is constant and has a diameter more than 2 cm. with an irregular internal border should make the examiner suspect carcinoma. At the best it can only be hoped to detect early cases.

Carcinoma involving the extrahepatic ducts is less frequent, there being only 100 cases in the series of Judd and Gray[23] (22,365 operations), and appears to be more frequent in the male (58 per cent, Judd and Gray,[23] and 61 per cent, Rolleston[28]). In the two cases in the 1932 group examined at the Mayo Clinic cholecystographically both were associated with non-functioning gall-bladder. One of the cases was a carcinoma of the ampulla of Vater, and it is just possible that had irregularity of the second part of the duodenum been found on barium meal examination in association with a non-functioning gall-bladder, a diagnosis of carcinoma of the ampulla of Vater could have been suggested. Carcinoma of the ampulla of Vater has been raised to the status of a definite clinical entity, and Gustav Pallin[29] has collected 16 cases.

V. DUODENAL AND GASTRIC ULCERS AS A CAUSE OF NON-FILLING OF THE GALL-BLADDER

Brailsford[30] and others have stated that in a certain number of cases of gastric and duodenal ulcer the gall-bladder fails to fill satisfactorily, and suggest that an opaque meal should be given in all non-functioning cases.

In a series of 184 operations on non-functioning gall-bladders duodenal ulcer was found in only 2 cases. One of these cases was associated with gall-stones and cholecystitis, and in the other I could find no report on the state of the gall-bladder, which was therefore presumably normal.

In a series of 127 cases of poorly-functioning gall-bladders duodenal ulcer was found in only 4 cases. Of these, 3 had associated stones and 1 had no gall-bladder lesion.

On the other hand, in a series of 350 investigated cases of normally functioning gall-bladders duodenal ulcer was found at operation in 60, or 17 per cent of the total.

In 1927 Kirklin[4] analysed 204 normally functioning gall-bladders and found :—

Duodenal ulcer	78
Gastric ulcer	5
Gastric and duodenal ulcer	5
Gastric carcinoma	2

Out of 1398 cases of good visualization, Ferguson and Palmer[52] found 209 cases of duodenal ulcer and 14 cases of gastric ulcer, giving a total of 16 per cent of cases with good shadow and ulceration of the duodenum or stomach.

The above data would appear to show that lesions of the stomach and duodenum play no part in interfering with the filling of the gall-bladder with dye. It is true that several series of cases have been reported from time to time in which

duodenal ulcer was found associated with gall-bladders that did not fill, but it must be remembered that most of the cases in which cholecystograms are made are patients who are suffering from indigestion, and the proportion of duodenal ulcers will be high. Certainly the above figures show a far higher percentage of duodenal ulcers in the cases in which the gall-bladder filled normally.

In cases of gross pyloric obstruction there may be delayed absorption of the dye and poor filling. In many of these cases, however, the dye can be seen in the stomach, casting a faint ill-defined shadow, and the radiologist's suspicions will be aroused.

VI. DISEASE OF THE LIVER AS A CAUSE OF NON-FILLING OF THE GALL-BLADDER

Barclay[1] has stated that one of the requisites for satisfactory filling of the gall-bladder by the Graham test is that the liver is functioning actively and excreting the salt. It is important to note that it is not necessary for the liver to be healthy and free from disease in order to do this, as is sometimes stated. So long as sufficient healthy liver tissue remains, a good cholecystogram should be obtained—probably only a small amount is necessary.

Of 219 cases of normally-functioning gall-bladder examined at the Mayo Clinic by operation, 3 cases were found in which the liver was seriously diseased. One showed a carcinoma of the liver, one was a case of cirrhosis, and the third was a case of splenic anæmia with associated hepatic cirrhosis.

Ferguson and Palmer,[52] in a series of 1398 cases of good visualization, found: 1 case of atrophic cirrhosis, 8 cases of catarrhal jaundice, and 3 cases of neoplasm of the liver.

In one case of may own the patient had slight jaundice at the time of examination and died some ten days later from subacute yellow atrophy, and yet the cholecystogram was of very good density.

VII. SIGNIFICANCE OF DELAYED EMPTYING OF THE GALL-BLADDER

Delayed emptying of a dye-filled gall-bladder is often considered as evidence of disease. In the first place it would seem likely that a gall-bladder which fills will always be capable of emptying.

Apart from this, when a gall-bladder does empty, the dye will pass into the bowel and then be re-absorbed and carried to the liver again just as the bile-salts are in the so-called entero-hepatic circulation. In fact a gall-bladder can be followed till it empties completely of dye, and provided the dye is not all got rid of by evacuation of the bowel it can be observed to appear again in the gall-bladder.

The logical conclusion to be drawn from a gall-bladder that remains filled for some time would appear to be that the patient has constipation and that the gall-bladder is healthy. Yet many radiologists still give a fat meal in order to see how rapidly the gall-bladder empties, and fail to realize that the purpose of this meal is to cause the gall-bladder to contract and so render visible small stones and tumours. As has been mentioned previously, adenomata rarely show till after the fat meal has been given (*see Figs.* 129–132).

Ivy and Oldberg[31] have succeeded in producing contraction of the gall-bladder by injection of an extract of intestinal mucosa which they call ' cholecystokinin ', and suggest that the fatty meal may stimulate the production of such a substance.

VIII. THE SIGNIFICANCE OF CALCIUM DEPOSIT IN THE GALL-BLADDER

Calcium is found deposited in stones, sometimes as the nucleus but more often as a ring enclosing a radiotranslucent stone, in the wall of the gall-bladder, or as amorphous calcareous débris in the interior of the viscus.

Romang[32] has shown by analysis of radiopaque material from the gall-bladder that this is almost always calcium carbonate, since calcium phosphate is present only in small amounts. Calcium bilirubinate stones contain so very little calcium that their absorption of X rays is only a little greater than that of water, while calcium carbonate is fifteen times greater than water.

In the case of stones the deposition of calcium in rings with the growth of the stone in the intervals between the rings, due to cholesterol and pigment, suggests that some very definite change must have occurred in the chemical composition of the gall-bladder contents. The most likely cause of this change is blockage of the cystic duct, and the following evidence seems to support this view.

A. L. Wilkie[33] carried out a series of interesting experiments on rabbits in the Surgical Research Department of the University of Edinburgh. The cystic duct was carefully ligated and streptococci were injected into the wall of the gall-bladder. When the animal was killed some time later the wall was thickened and fibrous, and the contents consisted of mucopurulent material with granular débris and calculi which contained a considerable quantity of calcium. On the other hand, when the experiment was repeated but the cystic duct left patent, the stones that formed were made up mainly of cholesterol and no calcium was found. (It is only fair to state, however, that Wilkie's work has been adversely criticized by Williams and McLachlan[34] and has not been confirmed.)

Johnston, Ravdin, Austin, and Morrison[35] studied the absorption of calcium from the bile-free gall-bladder. Dogs were used and the cystic duct was ligated but the vessels and lymphatics were left intact. They reported from their observations that they would conclude that calcium is not secreted into the gall-bladder when the wall is normal, but that a small amount may be secreted when the viscus is damaged.

Phemister, Day, and Hastings,[36] from experiments on animals, concluded that the requirements necessary for the deposition of calcium in the gall-bladder were: (1) Obstruction of the cystic duct; and (2) Low-grade chronic inflammation. They further state that the chemical composition of the gall-bladder contents under these circumstances becomes altered and calcium accumulates to such an extent that supersaturation results and the calcium is deposited.

Blockage of the duct may occur by impaction of a stone either in the duct itself; or in Hartmann's pouch (a lateral pouching at the junction of the cystic duct and gall-bladder); or by inflammation, for the cystic duct is 1½ in. long and is only ⅛ in. in diameter, and its lumen is further narrowed by Heister's valves; or lastly by tumour originating in the vicinity of the outlet.

Phemister, Rewbridge, and Rudisill[37] reported seven cases of calcium carbonate

deposit in the wall of the gall-bladder, the cystic duct of which was obstructed by stone or inflammation in every instance, and stated that there is generally no bile in such gall-bladders. The bile is probably all absorbed just as it is in those cases already mentioned in which the common bile-duct is obstructed and 'white bile' is formed.

Whipple,[38] of New York, reported a case of calcium carbonate paste in the gall-bladder, the cystic duct of which was obstructed by carcinoma.

Fowler[39] reported a case of calcified gall-bladder with complete obstruction of the cystic duct.

Grey Turner[9] states that calculi with a large proportion of calcium are most frequently formed in closed infected gall-bladders.

Volkmann[40] suggests that in cases of 'Kalkmilchgalle' (lime-water bile), the calcium may have been secreted by the gall-bladder when the cystic duct is obstructed.

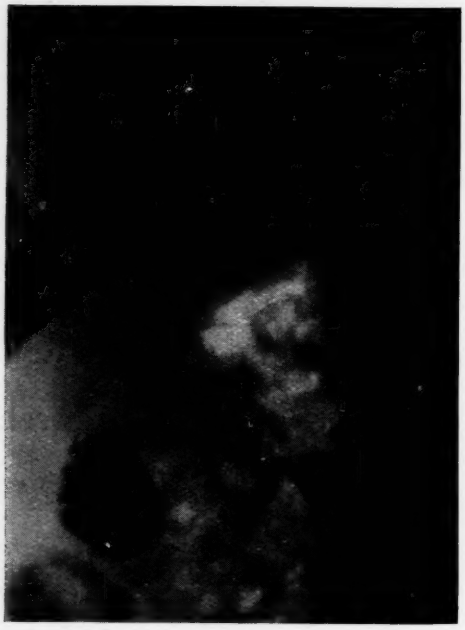


FIG. 136.—Note the stone in the cystic duct and no dye in the gall-bladder.

Phemister, Rewbridge, and Rudisill[37] reported three interesting cases in which a stone blocked the cystic duct and calcium was deposited only on the gall-bladder side of the stone.

Phemister, Day, and Hastings[36] studied 11 cases of obstruction of the cystic duct and found that 6 had mild chronic cholecystitis with a separate deposit of calcium carbonate in the gall-bladder. The remaining 5 cases had no calcium carbonate precipitation but showed more marked inflammation with serous exudation and the ordinary picture of hydrops.

The above references show that cystic-duct obstruction and calcium deposition in the gall-bladder are frequently found associated (*Fig.* 136). But it must not be considered that when calcium is seen casting a shadow in the gall-bladder that the cystic duct will be occluded in all cases, for at the time of examination the obstruction may have been overcome by passage of the stone, by its slipping back into the gall-bladder, or by diminution of the inflammatory swelling in the region of the duct. Such factors make operative and post-mortem findings difficult to evaluate (*Figs.* 137–141).

Turning to the evidence obtained by cholecystography alone, it is a well-known finding that calcareous débris and calcification of the wall of the gall-bladder are, in almost every case, associated with non-filling of the gall-bladder following administration of the dye (*Figs.* 142, 143). In the 1932 series over 20 per cent of the stones visualized had calcium deposited in them, and in 22 per cent of cases the stones cast primary shadows and the gall-bladder was reported as non-functioning (*Fig.* 144). An example of calcification only on the gall-bladder side of the stone

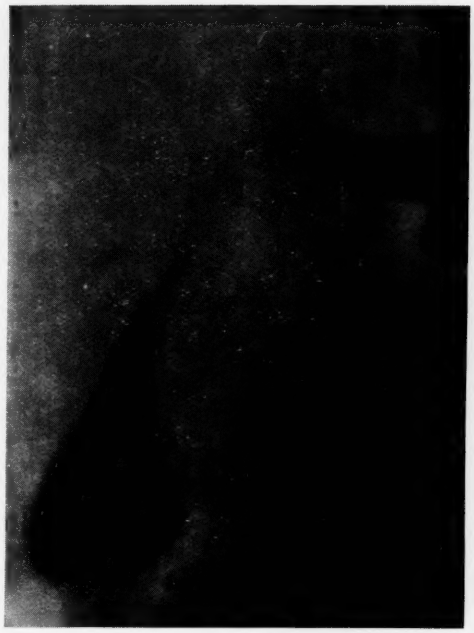


FIG. 137.—Calcified stone in dye-filled gall-bladder. The interpretation placed on this is that the cystic duct previously blocked during the formation of the stone, has now become patent.

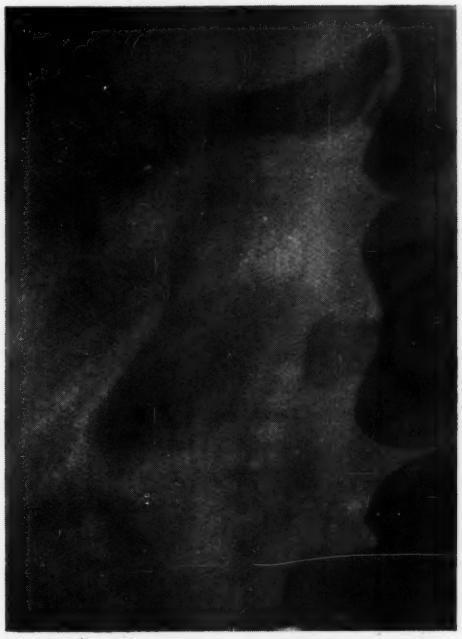


FIG. 138.—Another example of opaque stones in a dye-filled gall-bladder. Interpretation similar to *Fig.* 137. Note small size of stones, which on removal were only 1 mm. in diameter.

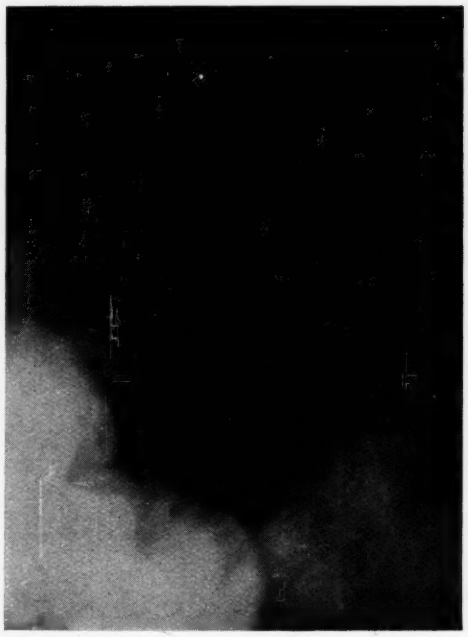


FIG. 139.—Interpretation: Gall-stones with radio-opaque centres formed when the cystic duct was occluded. Periphery of radiotranslucent material formed since cystic duct has become patent. Note dye in gall-bladder.

FIG. 140.—Interpretation: two radiotranslucent stones form the centre and are combined into one stone by calcified material in the gall-bladder, the cystic duct of which has again recently become patent as is shown by the presence of the dye.

FIG. 141.—Gall-stone indicating intermittent obstruction of the cystic duct and calcification alternating with deposition of cholesterol.

FIG. 142.—Calcareous débris at fundus of gall-bladder with 'fluid level'. The shadow above this is not due to dye but is a primary shadow which did not increase on administering dye.

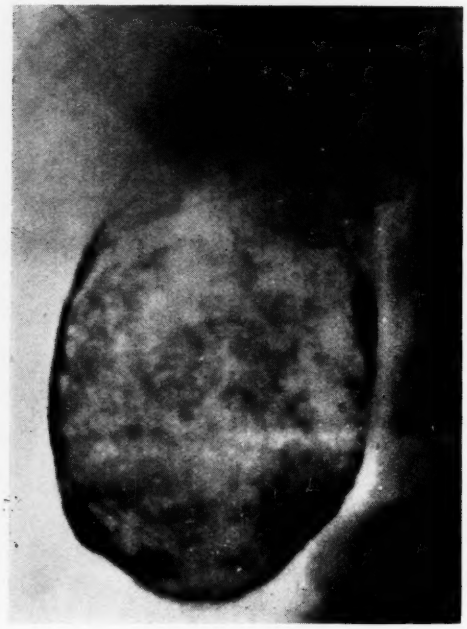


FIG. 143.—Gall-bladder with calcified walls. No dye entered it.

in the cystic duct is given in *Fig.* 145. In the normally-functioning gall-bladder with stones calcium deposition is comparatively rare.

It will be noted that judging from the size of the stones and the size and thickness of the calcified rings, one obtains the impression that the calcium deposition has occurred in all the stones at the same time and for the same length of time as the result of some sudden change in the biliary content from which, of course, the stones grow. An example, too, of primary calcium stones is given, and they will all be noted to be of the same size (*Figs.* 146, 147).

Andrews, Schoenheimer, and Hrdina[22] have shown fairly conclusively that cholesterol is deposited or crystallized out by withdrawal of the bile-salts from the gall-bladder contents. Normally in man the bile-salt cholesterol ratio is 20 to 1, and when the ratio falls below 13 to 1 cholesterol can no longer remain in solution (cholesterol is quite insoluble in water, and in the bile is dependent on the presence of bile-salts for its solution). Analyses of mixed gall-bladder bile in a post-mortem series of thirty stone-containing gall-bladders showed that the cholesterol content was 400 mgrm. and the bile-salt content 247 mgrm. per 100 c.c., or a bile-salt cholesterol ratio of 0·6. It will be noted that the cholesterol content is about normal and it is the bile-salt content which is markedly reduced.

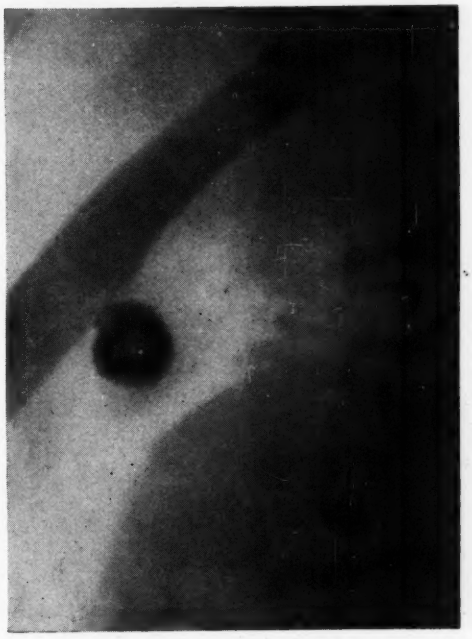


FIG. 144.—Calcified stone in a gall-bladder in which there is no dye.

While the normal bile-salt cholesterol ratio in man is perilously near the precipitation point, the ratio in animals is much higher and cholesterol stones are not normally found. In dogs the ratio is 100 to 1. Following Naunyn's[25] experiments Walsh and Ivy,[36] using dogs, and later Phemister, Day, and Hastings,[36] using rabbits, showed that human gall-stones may actually be absorbed if placed in the gall-bladders of those animals. These experimental conclusions show the great importance of the rôle played by the bile-salts, and the value of those findings is enhanced by the work of Andrews, Schoenheimer, and Hrdina,[22] who found that in the infected gall-bladder bile-salts are absorbed rapidly and cholesterol very slowly if at all. This confirms the work of Neuman.[41] In the healthy gall-bladder, on the other hand, there is no differential absorption.

From the above evidence the following deductions can apparently be made. Under ordinary circumstances, with the cystic duct patent, gall-stones consisting mainly of cholesterol grow. But in order to grow the cholesterol stones must be constantly supplied with fresh bile entering by the cystic duct. Similarly, pigment stones grow by deposition of pigment from the bile, as is well seen in cases of hæmolytic jaundice. If the cystic duct is blocked it becomes evident that those

FIG. 145.—Gall-stones with no dye in gall-bladder and stone in cystic duct with calcification only on gall-bladder side. The interpretation given here is that the radiotranslucent centres were formed when the cystic duct was patent. The stone in the cystic duct now prevents any further cholesterol from entering, and the calcium in the inflammatory exudate has become concentrated and deposited on the stones. The upper margin of the stone in the cystic duct is not subjected to those changes and is not calcified.

FIG. 146.—Calcium deposition on stones. Note that the size and thickness of the rings are approximately the same, indicating that calcification has occurred for the same length of time and at the same time in all the stones.

FIG. 147.—Primary calcium stones. Note that the stones are all of the same size. Some dye has entered the gall-bladder, indicating that the cystic duct is now patent.

stones must cease to grow, as it is rarely any longer considered that the wall of the gall-bladder secretes cholesterol—in fact the work of Andrews, Schoenheimer, and Hrdina[22] is quite against this view.

When the cystic duct has become blocked and there is associated chronic mild inflammation, there will be passed into the gall-bladder a steady stream of inflammatory exudate which contains calcium. If the gall-bladder cannot expand, as it frequently cannot do, because of the fibrosis of its walls, fluid must be absorbed and the calcium content will increase and precipitation occur on the stones or wall of the gall-bladders (*Fig.* 148). The photograph (*Fig.* 145) showing calcification only on the gall-bladder side of the stone would appear to be good evidence in favour of this view being correct. In a more or less healthy gall-bladder with

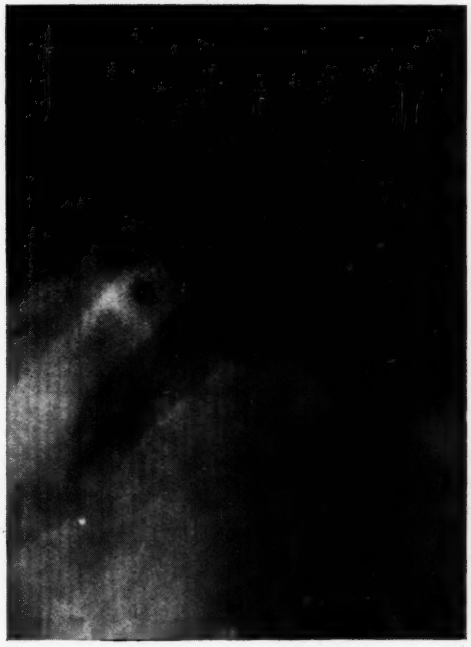


FIG. 148.—Calcified gall-stones. In the original film the outline of the gall-bladder can be easily seen without dye and this would indicate a high concentration of calcium in the fluid contents of the gall-bladder.

blockage of the cystic duct the viscus will expand to give the picture of hydrops and there will be no concentration of the calcium to any extent and therefore no deposition. If, on the other hand, the infection in the gall-bladder is acute and its duct is blocked, the condition of empyema will result. In fact when Andrews[42] examined the calcium content of the bile from acutely inflamed gall-bladders he found it to be low.

In an old untreated empyema of the chest calcification frequently occurs as a late process and is probably due to similar factors—namely, chronic inflammation acting in a cavity and leading to concentration of the inflammatory exudate poured in. If, on the other hand, the empyema is drained, and even although it keeps draining for years, calcification is rare because the inflammatory exudate is drained away and cannot be sufficiently concentrated to throw the calcium out of solution.

Similarly, calcification of an abscess rarely occurs if it is opened and drained, but may occur if no drainage is established.

It has been generally considered for a long time that while cholesterol stones are found unassociated with evidence of inflammation, calcium stones always indicate previous infection. The former statement is open to doubt, but the association between inflammation and calcium stones is admitted by all. It is precisely in those cases that blockage of the cystic duct is liable to occur.

IX. THE FREQUENCY OF CARCINOMA IN CASES WITH GALL-STONES

E. A. Graham[43] states that carcinoma of the gall-bladder constitutes 8 to 10 per cent of all cases of carcinoma in the female, and draws this conclusion from autopsy tables compiled by von Berencsy and von Wolff.[44] Graham[43] also states that from these tables it will be seen that carcinoma of the gall-bladder is three times as frequent as carcinoma of the lip, about twice as frequent as carcinoma of the rectum, of about the same frequency as carcinoma of the breast, and a little less than half as frequent as carcinoma of the stomach. From the above figures Graham concludes that the operative risk of removal of gall-stones is much less than the risk of the patient developing carcinoma of the gall-bladder.

Lentze[45] found in female patients over 39 years of age who had gall-stones that there was associated carcinoma in 5·1 per cent of cases. Rolleston[28] states that 4·5 per cent of all cases of cholelithiasis are accompanied by carcinoma. Moynihan[46] gives 5 per cent, Riedel[47] 7 to 8 per cent, Mayo-Robson[48] 10 per cent, Schröder[49] 14 per cent, and Graham[43] himself 8·5 per cent of all cases, and later states that "it would seem reasonable to conclude, however, that at least 4 or 5 per cent of all women in the cancer age who have gall-stones will develop carcinoma of the gall-bladder, and perhaps further study will show that it may actually be much higher."

These figures are indeed alarming and would mean that when gall-stones are recognized by the radiologist one out of every ten to twenty cases had carcinoma of the gall-bladder. It would be a serious error for the radiologist to miss one single case of gall-stones, for obviously all gall-bladders with stones would require to be removed immediately by operation.

In the 22,365 operations on the biliary tract at the Mayo Clinic, Judd and Gray[23] found stones in 15,422 cases and carcinoma of the gall-bladder in 212 cases, giving an incidence of malignancy of 1·3 per cent in all cases of gall-stones operated on. But they also state that in all cases in which the possibility of carcinoma was suspected operation was performed, but not all cases of gall-stones were operated on, so that the percentage should possibly be still lower.

In the cholecystographic data for 1932, stones were found at operation in 415 cases. Of these there were 2 cases of carcinoma of the gall-bladder, giving an incidence of 0·48 per cent.

Leitch[50] states that the lowest incidence reported is that of Candler,[51] who found, in post-mortem statistics from an asylum practice, an incidence of only 2 cases of carcinoma in 315 cases of calculi (0·6 per cent).

It seems difficult to believe that carcinoma of the gall-bladder is three times as frequent as carcinoma of the lip and of about the same frequency as carcinoma

of the breast. If these statements were true, surely carcinoma of the gall-bladder would be found far more frequently. Probably the explanation of the statements of Graham[43] is to be found in the fact that they are based on post-mortem statistics, which have frequently been shown to be highly unreliable. Operation statistics ought to be better, but probably the best figures will ultimately be obtained from the study of cholecystographic data and their correlation with operative findings. So far as the above radiological evidence goes, it does not support such a high incidence and is more in keeping with what one would expect on broad consideration of the subject.

Finally, it must not be concluded that the view is taken that gall-stones do not produce cancer, for it would seem that most of the evidence is in favour of this theory and most cases of carcinoma of the gall-bladder are accompanied by stones.

SUMMARY AND CONCLUSIONS

1. A standard method of roentgenological reporting of cholecystograms has been given.

2. The technique of administration of the dye as followed at the Mayo Clinic has been outlined, and it would appear that the oral technique, if carefully carried out as suggested, is just as accurate as the best results obtained by the intravenous method of administration.

3. The cholecystographic data for 1932, consisting of 732 cholecystograms all checked by operation, have been analysed and the accuracy obtained in the various groups expressed. The interpretation of the terms ' poorly-functioning ' and ' non-functioning ' in terms of pathology has been given. Various possible errors in interpretation have been pointed out.

4. The roentgenological basis of the diagnosis of tumours, both simple and malignant, has been discussed and the differential diagnosis given.

5. Peptic ulcer of the stomach and duodenum has been shown to play no apparent part in interfering with the filling of the gall-bladder.

6. The importance of realizing that a good cholecystogram does not rule out even extensive and serious disease of the liver has been demonstrated.

7. Delayed emptying of the gall-bladder should not be regarded as evidence of disease.

8. Deposition of calcium in the gall-bladder is evidence of the fact that at the time of its deposition the cystic duct was blocked, but it must also be noted that calcium deposit does not always indicate that the cystic duct is blocked at the time of examination, as patency of its lumen may have been restored. If the above suggestion is accepted it would indicate that calcified gall-stones form a greater indication for operation than those which are not calcified.

9. From the evidence obtained the suggestion is put forward that gall-stones are accompanied by carcinoma of the gall-bladder in probably less than 1 per cent of cases.

In conclusion, I wish to state that much of the material in this paper concerning (1) technique, (2) statistical review of cholecystographic data, and (3) the important points in the diagnosis of tumours of the gall-bladder, was obtained from perusal of articles written by Dr. B. R. Kirklin, but I think I am justified in quoting them in full rather than only giving references, as his work is not so well known in Britain as in America.

I am deeply indebted to the Mayo Foundation for the facilities they have given me in writing this paper and for the opportunity I have had to study the enormous amount of material which exists in the Mayo Clinic. I especially wish to thank Dr. B. R. Kirklin for the information he has placed at my disposal and for the assistance he has given me.

REFERENCES

[1] BARCLAY, A. E., *The Digestive Tract*, 1st ed., 1933. Cambridge University Press.

[2] CAYLOR, H. D., and BOLLMAN, J. L., "The Bilirubin Content of the Gallbladder in Cholecystic Disease", *Arch. Pathol. and Lab. Med.*, 1927, iii, 993.

[3] KIRKLIN, B. R., "The Efficiency of Cholecystographic Diagnosis", *Jour. South Carolina Med. Assoc.*, 1932, xxviii, 311. "Persisting Errors in the Technic of Oral Cholecystography: A Procedure Designed to Avoid Them", read before the American Medical Association, Milwaukee, June, 1933.

[4] KIRKLIN, B. R., "The Normal Cholecystographic Response", *Radiology*, 1928, July.

[5] LEVYN, L., "An Effective Gallbladder Stimulant to Supplant the Fat Meal", *Amer. Jour. Roentgenol.*, 1931, xxvi, 904.

[6] DELARIE, A. J., "Paths of Absorption and Excretion of Sodium Tetraiodophenolphthalein", *Jour. Lab. and Clin. Med.*, 1931, xvi, 329.

[7] GRAHAM, E. A., et al., *Diseases of the Gall-bladder and Bile Ducts*, 1929. London: Baillière.

[8] HAWLEY, S. J., "Comparison of Intravenous and Oral Cholecystography", *Amer. Jour. Roentgenol.*, 1931, xxvi, 232.

[9] CHOYCE, C. C., and BEATTIE, J. M., *A System of Surgery*, 3rd ed., 1932, ii. Cassell & Co., Ltd.

[10] NICKEL, A. C., and JUDD, E. S., "Cholecystitis: A Bacteriological and Experimental Study of 300 Surgically Resected Gallbladders", *Surg. Gynecol. and Obst.*, 1930, l, 655.

[11] PFAHLER, quoted by G. E. Vilvandré, *Brit. Jour. Radiol.*, 1932, v, 241.

[12] ROWDEN, quoted by G. E. Vilvandré, *Ibid.*

[13] SHERREN, quoted by G. E. Vilvandré, *Ibid.*

[14] POTTER, H. E., "Gall-stones Confused with Colon Diverticula", *Amer. Jour. Roentgenol.*, 1932, xxviii, 803.

[15] LINDSAY, quoted by G. E. Vilvandré, *Brit. Jour. Radiol.*, 1932, v, 241.

[16] CAMP, J. D., BALL, R. G., and GREENE, C. H., "Calcification of the Suprarenal Glands in Addison's Disease", *Amer. Jour. Roengenol.*, 1932, xxxviii, 594.

[17] KIRKLIN, B. R., "Cholecystographic Diagnosis of Neoplasms of the Gall-bladder", *Amer. Jour. Roentgenol.*, 1933, xxix, 8.

[18] KAUFMANN, EDUARD, *Lehrbuch der speziellen pathologischen Anatomie*, 1922, 767. Berlin: Walter de Gruyter & Co.

[19] ERWIN, H. C., and MACCARTY, W. C., "Papilloma of the Gall-bladder", *Ann. of Surg.*, 1915, lxi, 725.

[20] BOYD, W., *Surgical Pathology*, 2nd ed., 1930. W. B. Saunders Co.

[21] ROSSI, A., "Atonic Gall-bladder and Strawberry Gall-bladder", *Amer. Jour. Roentgenol.*, 1932, xxvii, 205.

[22] ANDREWS, E., SCHOENHEIMER, R., and HRDINA, L., "Etiology of Gall-stones—Chemical Factors and the Rôle of the Gall-bladder", *Arch. of Surg.*, 1932, xxv, 796.

[23] JUDD, E. S., and GRAY, H. K., "Carcinoma of Gall-bladder and Bile Ducts", *Surg. Gynecol. and Obst.*, 1932, lv, 308.

[24] ZENKER, H., "Der primaere Krebs der Gallenblase und seine Beziehung zu Gallensteinen und Gallenblasennarben", *Deut. Arch. f. klin. Med.*, 1888, xliv.

[25] NAUNYN, quoted by J. G. Sherrill, "Cancer of the Gall-bladder and Ducts", *Ann. of Surg.*, 1906, xliv, 866.

[26] MUSSER, J. H., "Primary Cancer of the Gall-bladder and Bile Ducts", *Boston Med. and Surg. Jour.*, 1889, cxxi, 581.

[27] TATERKA, HEINZ, "Cholezystographische Untersuchungen Mittels 'Decholindennung' und 'Eigelbentleerung'", *Röntgenpraxis*, 1931, iii, 721.

[28] ROLLESTON, H., and MCNEE, J. W., *Diseases of the Liver, Gall-bladder and Bile Ducts*, 3rd ed., 1929, 738. London: Macmillan & Co.

[29] PALLIN, G., "Das Carcinom des Ductus Hepatico-Choledochu und seine chirurgische Behandlung", *Beitr. z. klin. Chir.*, 1921, cxxi, 84.

[30] BRAILSFORD, J. F., "Discussion of Cholecystography", *Proc. Roy. Soc. Med.*, 1932, xxv, 1249.
[31] IVY, A. G., and OLDBERG, G. E., "Contraction and Evacuation of the Gall-bladder by Purified 'Secretin' Preparations", *Amer. Jour. Physiol.*, 1928, lxxxvi, 599.
[32] ROMANG, F., "Beitrage zur Röntgendiagnostik der Cholelithiasis", *Forts. Roentgenstrahlen*, 1927, xxxv, 119.
[33] WILKIE, A. L., "The Bacteriology of Cholecystitis. A Clinical and Experimental Study", *Brit. Jour. Surg.*, 1928, xv, 450.
[34] WILLIAMS, B., and MCLACHLAN, D. G. S., *Lancet*, 1930, ii, 342.
[35] JOHNSTON, C. G., RAVDIN, I. S., AUSTIN, J. H., and MORRISON, J. L., "Absorption of Calcium from Bile-free Gall-bladder", *Amer. Jour. Physiol.*, 1932, xcix, 648.
[36] PHEMISTER, D. B., DAY, L., and HASTINGS, A. B., "Calcium Carbonate Gall-stones and their Experimental Production", *Ann. of Surg.*, 1932, xcvi, 595.
[37] PHEMISTER, D. B., REWBRIDGE, A. G., and RUDISILL, H., "Calcium Carbonate Gall-stones and Calcification of the Gall-bladder following Cystic Duct Obstruction", *Ibid.*, 1931, xciv, 493.
[38] WHIPPLE, A., quoted from Phemister, Rewbridge, and Rudisill.
[39] FOWLER, W. F., "Calcareous Changes of the Gall-bladder Wall", *Ann. of Surg.*, 1923, lxxviii, 623.
[40] VOLKMANN, J., "Ueber kalkmilch artige Galle", *Deut. med. Woch.*, 1926, lxxiii, 2014.
[41] NEUMAN, G. E., "Beitrage zum Studium der Gallenniederschlags und Gallensteinsbildung", *Beitr. z. pathol. Anat.*, 1931, lxxxvi, 187.
[42] ANDREWS, S. E., "Detailed Studies of a series of Gall-bladder Cases", *Surg. Gynecol. and Obst.*, 1933, lvii, 36.
[43] GRAHAM, E. A., "Prevention of Carcinoma of Gall-bladder", *Ann. of Surg.*, 1931, xciii, 317.
[44] VON BERENCSY, G., and VON WOLFF, K., "Ueber die Verbreitung des Carcinoms auf Grund von 19,908 Sektionen des St. Stephanspitals in Budapest", *Zeits. f. Krebsforsch.*, 1924, xxi, 109.
[45] LENTZE, F. A., "Gallensteine und Gallenblasen Carcinom", *Beitr. z. klin. Chir.*, 1926, cxxxvii, 38.
[46] MOYNIHAN, quoted from Leitch.
[47] RIEDEL, quoted from Leitch.
[48] MAYO-ROBSON, quoted from Leitch.
[49] SCHRÖDER, quoted from Leitch.
[50] LEITCH, A., "Gall-stones and Cancer of the Gall-bladder: An Experimental Study", *Brit. Med. Jour.*, 1924, ii, 45.
[51] CANDLER, quoted from Leitch.
[52] FERGUSON and PALMER, *Jour. Amer. Med. Assoc.*, 1933, March 18, 809.

AN UNUSUAL TUMOUR OF THE NECK

By R. E. NORRISH

SURGICAL REGISTRAR, ROYAL NORTHERN HOSPITAL

THE uncommon features presented by a solid tumour removed from the lateral aspect of the neck are believed to be of sufficient interest to warrant the placing of the following case on record.

The patient was a man, aged 62 years, who came to the hospital complaining of a swelling behind the angle of his lower jaw. He first noticed it five years previously; it was painless and was gradually increasing in size.

A movable tumour was present, in size a little smaller than a hen's egg. It was firm in consistency, non-fluctuant, and there was no evident fixation to adjacent structures. Under general anæsthesia the tumour was exposed through a transverse incision. It lay beneath the deep cervical fascia, projecting forward from under cover of the sternomastoid, and extending upwards as far as the lower pole of the parotid gland. (No definite attachment, however, to the latter was demonstrated.) It was easily enucleated from its surrounding capsule. The specimen obtained was ovoid in form, and covered by a thin membrane in which a number of blood-vessels were to be seen. Its cut surface was greyish-yellow in colour, with one or two small areas of softening. Microscopically (*Figs.* 149, 150) there were evident a large number of alveoli, most of them small in size, but a few almost reached the size of small cysts. Each was lined by a well-marked epithelium of very uniform type throughout the section. This was constituted by a double layer of cells, the inner being columnar in form, and the outer cuboidal. Here and there the epithelium projected into the alveoli, forming processes which occasionally showed branching. The cells were non-ciliated. Surrounding these alveoli and extending between them was lymphoid tissue, densely packed and with germinal centres, and around the whole a fibrous capsule was evident. No muscle or cartilage was found in the sections, and no sebaceous gland, hair follicle, or Hassal formations were seen.

In 1898, Neisse[1] described the inclusion of parotid tubules in lymphatic glands. The developing salivary buds are at an early stage surrounded by a diffuse mass of lymphoid tissue which gradually becomes collected into nodes, and around these, capsules are eventually formed. During this process certain salivary epithelial tubules may become separated and included within the lymphatic gland. These formations were demonstrated by Neisse in many newly-born infants, and they have also been shown in association with the submaxillary salivary gland. It is from these remnants that a tumour is believed occasionally to arise.

During the past twenty-five years there have been described a number of cases bearing a close resemblance to each other. Two cases were described by Albrecht and Artz,[2] who pointed out the striking resemblance of the included epithelium to that of salivary duct. This view is endorsed by G. W. Nicholson,[3] who presents two more examples. Ten cases are reviewed by Moatti,[4] and this writer points

out that all have certain properties in common: the swellings are all situated either within the parotid gland or just below it, behind the angle of the jaw, are encapsulated beneath the deep cervical fascia, and are easily enucleated. Histologically they all

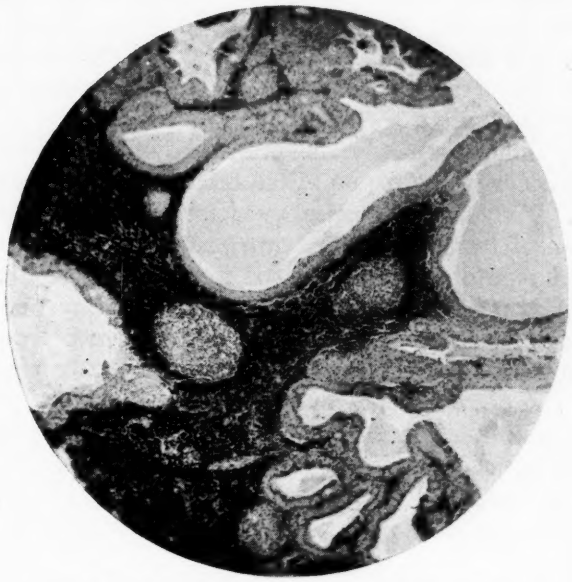


FIG. 149.—Section of tumour removed (low power).

FIG. 150.—Section of tumour removed (high power).

show alveolar formation surrounded by lymphoid tissue with well-marked germinal centres. The alveoli usually have a double epithelial layer, the inner being columnar. Some of the alveoli are large and form cystic spaces, into which papillary processes may project.

The case described above is in accord with almost all these features, though the lymphoid tissue is in places rather sparse and seems to be crowded out by the large number of alveoli.

The precise origin of these swellings is undecided. On histological grounds Nicholson believes that they are adenomata of salivary origin contained within lymphatic glands, and he calls them 'adenomata of præ-parotid glands'. This view has received considerable support, and the term 'lympho-glandular cystoma' is mentioned by certain writers.

It is, though, difficult to deny the possibility of a branchial origin to these tumours, for they occur in the region of the neck where branchial remnants are so commonly found. They contain elements which are found in branchial derivatives, and the association of lymphoid tissue with pharyngeal outgrowth is well known. In the entodermal type of branchial cyst it is not uncommon to find occasional Hassal's corpuscles, small amounts of cartilage, or striped muscle. It is noteworthy that these structures have not been mentioned in the small series of cases quoted above, and certainly none was evident in the sections of the tumour removed in the case described. The occurrence, too, of columnar epithelium in a tumour so near the surface, is unusual in a branchial cyst, for this is essentially the situation of the more usual variety with its stratified squamous epithelium (Hamilton Bailey[5]).

These considerations lend weight to the suggestion that the tumours are not of branchial derivation, and their origin from salivary remnants is more probable.

I am indebted to Mr. L. E. Barrington-Ward for permission to publish this case, and to Dr. A. H. Robb-Smith and Dr. P. O. Ellison for their assistance with the histology of the tumour.

REFERENCES

[1] NEISSE, R., *Anatomische Hefte*, 10, 1898, Abt. 1, 287.
[2] ALBRECHT, H., and ARTZ, L., *Frankf. Zeits. f. Pathol.*, 1910, iv, 47.
[3] NICHOLSON, G. W., "Studies in Tumour Formation", *Guy's Hosp. Rep.*, 1922, 352; *Ibid.*, 1923, 43.
[4] MOATTI, L., "Les Fistules et les Kystes congénitaux de la Région latérale du Cou", *Thèse de Paris*, 1929, 151.
[5] BAILEY, HAMILTON, *Branchial Cysts*, 1927, 4. London.

EXPERIMENTAL SURGERY

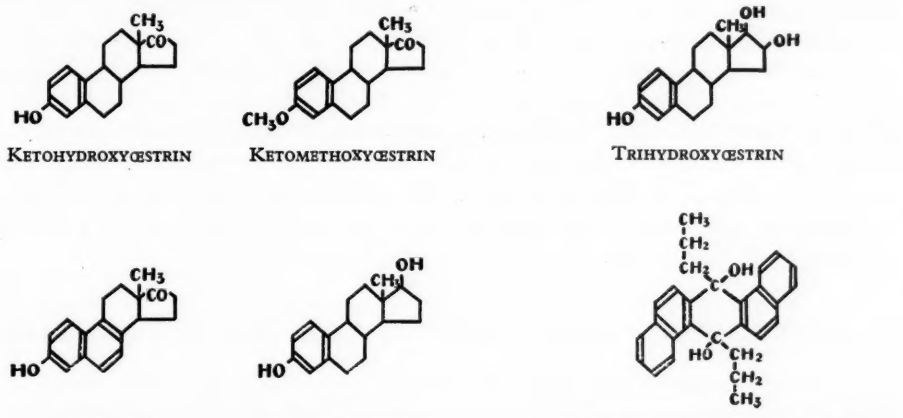
PATHOLOGICAL CHANGES INDUCED IN THE MAMMA BY ŒSTROGENIC COMPOUNDS

By HAROLD BURROWS, C.B.E.

RESEARCH INSTITUTE, THE CANCER HOSPITAL (FREE), LONDON.

(*Being a Hunterian Lecture delivered at the Royal College of Surgeons of England on January 14th, 1935*)

THE regulation of the structure and function of the mamma by hormones elaborated in other organs of the body has long been recognized. Thirty years ago Halban showed ground for supposing that the increase of the breast at puberty was secondary to the awakened activity of the ovary at this period, and that the enlargement of the mamma in pregnant women and in newly born babies of either sex was caused by some substance derived from the placenta. His conclusions have been established by subsequent experimental inquiry.



KETOHYDROXYŒSTRIN — KETOMETHOXYŒSTRIN — TRIHYDROXYŒSTRIN

EQUILENIN — DIHYDROXYŒSTRIN — 9 : 10-DIHYDROXY-9 : 10-DI-*n*-PROPYL-9 : 10-DIHYDRO-1 : 2 : 5 : 6-DIBENZANTHRACENE

FIG. 151.—Structural formulæ of œstrin and some allied œstrogenic compounds.

Investigations in the laboratory have shown that mammary changes are brought about by hormones derived from the ovarian follicles and placenta, and perhaps from other sources. These hormones belong to a group of chemical compounds which exercise a remarkable influence on certain organs in the body, especially those concerned with reproduction, both in the male and in the female. *Fig.* 151 displays the structural formulæ of some of the œstrogenic substances the biological properties of which have been under examination in our laboratories. It will be seen that they have a general similarity of structure. They may be referred

to collectively as 'œstrogens', because they all produce in mice and rats those changes in the vagina which are associated with œstrus in these animals, and which, with ease and certainty, can be recognized by the microscopical examination of smears taken from the vagina at successive intervals of time.

Of these œstrogens the best known is ketohydroxyœstrin or œstrin, with which the greater part of the present paper will be concerned. The recognized changes induced in the female mamma by amounts of œstrin which are not excessive or too long continued—that is to say, the physiological effects—are an increase of the fat-containing stroma, with proliferation and dilatation of the ducts. In mice œstrin appears to have little or no direct influence in the induction of lactation, this being dependent upon hormones derived from the corpus luteum, the anterior hypophysis, and possibly elsewhere. The normal function of œstrin, so far as concerns the mamma of the female mouse, appears to be confined to a preparation of this organ, so that lactation subsequently may be brought about by the action of other hormones. No further reference will be made now to what may be regarded as the physiological functions of œstrin, our present purpose being to consider the part which this hormone can play in the causation of pathological lesions of the breast. The experimental investigations of various inquirers on this subject fall into two distinct groups, according to whether the tests were made with purified œstrin or not.

Before 1929, in which year Doisy, Veler, and Thayer, and also Butenandt, showed how œstrin might be separated in a crystalline form from the urine of pregnant women, all experimental work in this field was carried out under a great disadvantage. The methods used, apart from mere observation of the course of nature, consisted of the removal or insertion of whole tissues, or the injection of crude extracts made from them. In such circumstances any results obtained could not be attributed with confidence to the presence or absence, excess or deficiency, of any one particular chemical substance. Some valuable knowledge was obtained by these indirect means, and it will be convenient, without presenting a complete historical review, to recall one or two of the conclusions reached, before considering the more exact data acquired by experimentation with œstrogens in a chemically pure state.

I. EXPERIMENTS MADE BEFORE THE ISOLATION OF ŒSTRIN

In 1916 Lathrop and Leo Loeb, using female mice of several different strains, some of the strains having a higher incidence of spontaneous mammary cancer than others, found that removal of the ovaries, if carried out before the age of 6 months, led to a pronounced decrease in the incidence of cancer of the breast in these animals, although it did not entirely prevent it. Furthermore, in the few cases in which cancer arose in castrated female mice, it appeared later in life than in non-castrated mice of the same strain. Castration of mice above the age of 6 months did not have any pronounced effect in preventing mammary cancer. Continuing these observations, Loeb published a second paper in 1919 which threw further light on the connection between ovarian activity and cancer of the breast, for he was able to show, with greater precision than before, a contrast between the results following early and late castration respectively. If the ovaries were removed from mice between the ages of 3 months and 5 months, cancer of

the mamma was almost entirely prevented. If the castration was done between the fifth and the seventh month, the cancer rate was diminished, and when cancer did appear it was at a later age on the average than in non-castrated mice. Removal of the ovaries after the eighth month of life had no effect in reducing the incidence of mammary cancer.

Cori followed up Loeb's investigations. He removed the ovaries from mice belonging to a strain in which 78 per cent of the females suffered from spontaneous mammary carcinoma. In 49 of these mice which had been castrated at ages varying from 2 to 6 months, and which lived to 19 months or more, mammary cancer developed in 5 only. The incidence of cancer in these mice was thus reduced, by castration in the first six months of life, from 78 per cent to 10 per cent. In a second series he castrated 100 mice belonging to the same strain just after weaning—that is to say, when they were between 15 and 22 days old. At the end of 10 months 86 were still alive, and 60 reached the age of 20 months. Not one of them suffered from mammary cancer; whereas at 20 months of age, tumours had appeared in 74 per cent of the untreated control mice belonging to the same strain.

W. S. Murray, in addition to confirming the effect of early castration in preventing mammary cancers in female mice, carried out some further experiments which might be regarded as the reverse of those of Loeb and Cori. He used a strain of mice among which 80 per cent of the untreated females eventually suffered from mammary carcinoma. Tumours of the mamma did not appear in the untreated breeding males of this stock. He castrated 210 mice of each sex belonging to this strain, when they were between 4 and 6 weeks old, and transplanted subcutaneously in the abdominal region of each male an entire ovary taken from a sister. His results are shown in *Table I.*

Table I.—The Effect of Castration on the Incidence of Cancer of the Breast in Mice (*W. S. Murray*)

	Number Observed	Number in Which Cancer of Breast Occurred	Percentage	Mean Age at which the Tumours Appeared
				Months
Untreated breeding females ..	479	367	80	10·5
Spayed females	210	36	17·1	17·5
Castrated males with ovarian transplants ..	210	15	7	14·4
Castrated males without ovarian transplants ..	241	0	0	–

Goormaghtigh and Amerlinck treated doe mice with daily subcutaneous injections of an œstrin-containing extract prepared, they state, according to the method used at that time by Zondek and Aschheim, and by Laqueur. The administration was continued for several months, each dose containing 6 rat units

of œstrogen. The usual change caused in the mamma by this treatment was a dilatation of the ducts and acini, which became very abundant. In some of the cystic dilatations the epithelium was atrophied; more often it showed proliferation, the ducts being sometimes converted into solid cords. Infiltration with leucocytes was not uncommon. The authors attribute both the epithelial proliferation and the presence of leucocytes in large part, though not entirely, to the retention of secretion. In some examples there was a proliferation of the ducts without dilatation; in these instances mitoses were abundant in the epithelium and the nuclei varied greatly in size. It was particularly noted that the changes produced by these extracts were not equally distributed throughout the mammæ; one part of a gland might appear normal, or nearly so, while another part showed pronounced alteration. Occasionally adenomatous formations developed and were visible to the naked eye, and in one case an encephaloid carcinoma arose.

II. EXPERIMENTS WITH ŒSTROGENS IN A CHEMICALLY PURE FORM

The results of the foregoing experiments are, on the whole, in accord with those obtained by more recent and exact investigations carried out with œstrin itself in an uncontaminated state. Lacassagne's work calls for particular recognition in this field. In an early experiment he gave weekly injections of crystalline benzoate of œstrin dissolved in sesame oil to 5 young mice, commencing when they were between 10 and 18 days old. Of these mice 3 were males and 2 were females. They belonged to a strain in which about 72 per cent of the untreated females eventually suffered from spontaneous mammary carcinoma, though none of the males belonging to this strain had been known to be thus affected. In every one of the 3 males treated by œstrin in this experiment cancer of the breast developed within six months, one of the mice having two separate tumours. Mammary cancer appeared also in one of the two females, at the early age of 4 months.

Additional results of a similar kind have been reported by Lacassagne in a second paper. In the same manner as before he administered œstrin to mice belonging to two different strains to which I shall refer as Strain A and Strain B. The untreated females of Strain A show an incidence of mammary carcinoma of 72 per cent, while only 2 per cent of the untreated females of Strain B suffer in this manner. Weekly injections of œstrin into mice of Strain A resulted in the appearance of mammary carcinoma in every one of 5 males so treated, and of one tumour in 7 females. With mice of Strain B, after a similar course of treatment, 2 among 8 males and 1 among 7 females eventually suffered from malignant mammary tumours; and the carcinomata appeared in this group of mice at a more advanced age than that at which it arose in mice belonging to Strain A. In yet another strain of mice treated with œstrin in the same way as those just mentioned, no mammary tumours developed. Lacassagne made the further interesting discovery that in mice of Strain A—that is to say, the mice among which spontaneous cancer of the breast was frequent among the untreated females—the œstrous cycle was regular, lasting five days, œstrus proper occupying about forty-eight hours. In Strain B, on the other hand, great variations in the cycle were noticed; œstrus was of short duration, occurred at irregular intervals, and was apt to pass unperceived, and diœstrus often lasted a week. It was observed also that an

injection of œstrin caused a rapid and prolonged œstral reaction of the vagina in mice of Strain A and only a fugitive response in those of Strain B. These facts, showing a contrast between the two strains in their reaction to œstrin, suggested to Lacassagne that the difference of cancer incidence in the two groups might be referred possibly to this difference of sensitivity toward the action of œstrin.

Another observer, Harde, also has noticed an unusually long period of œstrus in two strains of mice in which mammary carcinoma is very common, and she states that exaggerated œstrus sometimes can be detected in mice carrying spontaneous mammary tumours.

Geschickter, Lewis, and Hartman administered repeated doses of œstrin to male monkeys and compared the mammary condition, as shown by material removed at a biopsy before the administration, with that found at the end of the experiment. They used 2 *Cebus* monkeys which were treated by subcutaneous doses of 500 rat units of œstrin (amniotin) for a period of ten days, and 5 *Macacus* monkeys which were treated in the same way for six weeks with smaller daily doses, the amounts of which are not clearly stated in their paper. Though the consequences were most pronounced in the latter series they were alike in character in all the 7 individuals. The mammæ were enlarged, and showed, when examined microscopically, an increase in length and dilatation of the ducts, an increase in the number of layers of epithelial cells lining them, and a proliferation of the periductal connective tissue. In other words, the monkeys all presented the appearances typical of cystic mastopathy, or, as it used to be called, ' chronic cystic mastitis '.

During the last two years experiments have been in progress at the Research Institute of the Cancer Hospital, with the object of elucidating the effects of œstrin when persistently administered over long periods of time. For an ample supply of pure œstrin we are indebted to the very great generosity of Dr. Girard.

The results about to be described are based on the microscopical examination of 312 mammæ taken from 199 mice, of which 28 were females and 171 were males. Of the 199 mice used, 130 had been treated with œstrin or some allied compound during a period of fifty days or more, and 69, including 53 males, were controls. Among the controls were 30 males which had received applications of benzene free from œstrogen in just the same manner as those treated with benzene in which some œstrogen was dissolved. The remainder of the male control mice had received either no treatment (13) or were mice which had been used for grafting with tumours (10).

The method used in the greater part of this work has been to apply œstrin, dissolved in benzene so as to make a 0·01 per cent solution, to the non-epilated skin of the mouse's back, in the interscapular region, by a single application of a small paint brush. These applications were made twice a week, and were continued usually until the death of the animal.

ANATOMICAL CONSIDERATIONS

The female mouse, though subject to individual variations, normally has five mammæ on each side. These are far less discrete and clearly circumscribed than is the human mamma, and, when fully developed, they extend over a large proportion of the subcutaneous layer of the animal's body. The most conspicuous nipple is the fourth, counting from before backwards, and is situated in the iliac

region. About 4½ mm. forwards and in a dorsal direction from this nipple, and surrounded by mammary tissue, is a lymphatic gland. This iliac lymphatic gland is almost constantly present in mice, and I have used it as a landmark for the mamma in both males and females. In every case a strip of skin and subcutaneous tissue has been taken, including this iliac lymphatic gland and the readily seen blood-vessels which lead from it towards the lumbar region. These blood-vessels are surrounded by a mass of fat which, in the female mouse, and sometimes in the male, contains mammary ducts and acini. No microscope section in which the iliac lymph-gland is not displayed has been used for statistical purposes in the present inquiry. *Fig.* 152 represents a section made in the way just described through the iliac lymphatic gland of an unmated doe, and shows the distribution of mammary ducts around the gland. *Fig.* 153 is a photograph of a similar section taken from a mouse which had recently littered. These illustrations are intended to justify, if possible, the selection of the iliac gland as a landmark for the mamma. And here an explanation will be necessary. The majority of our experiments have been carried out on male mice; and although the mamma of the male is in some respects more suitable than that of the female for studying the effects of œstrogens, yet in the mouse there is one serious disadvantage—namely, the absence from the male of any nipple, areola, or other external sign to mark where the mammary rudiments are to be found. The iliac lymph-gland, therefore, was chosen as a landmark merely because no better one was discovered. The only alternative seemed to be the making of serial sections in every case, and this was not practicable. Some justification for the choice of the iliac gland as a landmark is required, because microscopical sections prepared in this way from normal untreated male mice only occasionally show any mammary tissue at all; and in the exceptional instances where mammary tissue is present it is extremely scanty. The mamma of the normal untreated male mouse consists only of a few very small vestigial ducts which are invisible to the naked eye (*Fig.* 154).

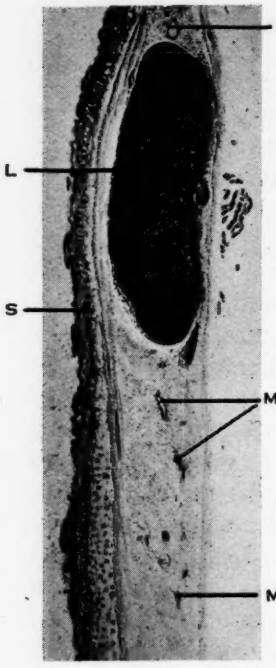


FIG. 152.—Section through fourth mamma of an old untreated, unmated female mouse. L, Iliac lymph-gland; M, Mammary ducts; S, Skin. (× 12).

Similar sections made from male mice which have been treated for a sufficient period with œstrin more often reveal mammary tissue, sometimes in abundance.

On the average about twenty sections of each mamma were examined, and if any one of these sections from a male mouse showed the presence of a duct, the result was recorded as positive. In some mice both iliac mammæ were examined, and in others only one. Among the treated mice it happened not infrequently that a pronounced development of mammary tissue might be seen in one of the mammary regions, while sections made from its fellow of the opposite side revealed no mammary tissue at all. Possibly in such instances no mammary vestige was present on that side, for anatomical variations occur, and one of the nipples and mammæ may be absent even in the female mouse. Probably also the iliac

lymph-gland has not an unvarying relationship with the nipple and vestigial mamma; and it is conceivable, too, that an extension of the vestigial ducts under the influence of œstrin might take some other direction than towards the iliac lymph-node.

In spite of the anatomical disadvantages entailed by using the iliac lymph-gland as a landmark for the mamma, the results of the method have been satisfactory from the practical standpoint.

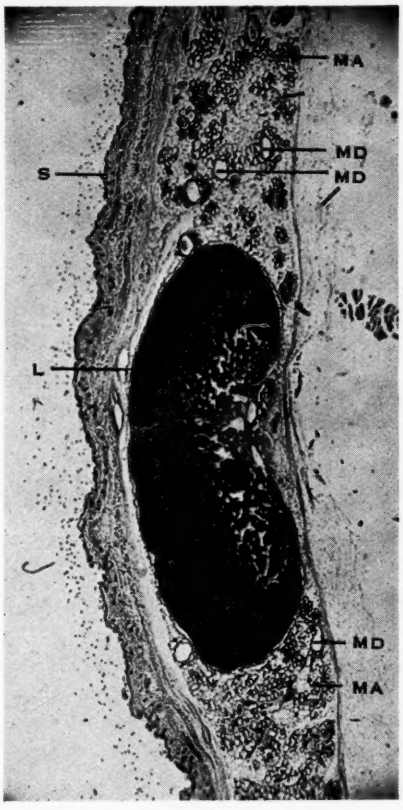


FIG. 153.—Section through fourth mamma of a mouse which had recently littered. Shows large number of mammary ducts and alveoli surrounding the iliac lymph-gland. S, Skin; L, Lymph-gland; MD, Mammary ducts (dilated); MA, Alveoli. (× 12.)

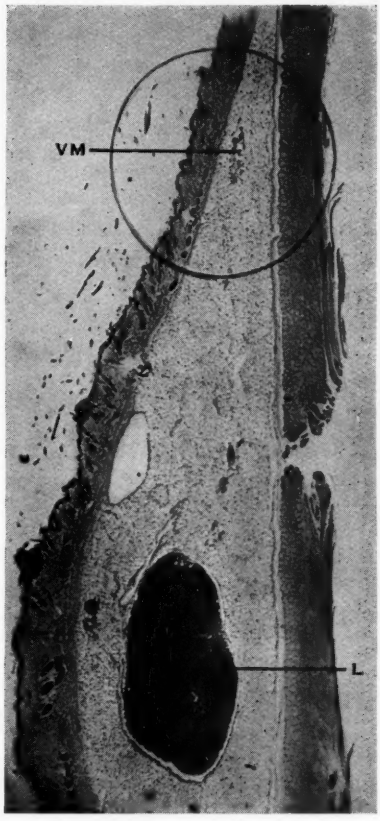


FIG. 154.—Section through the iliac lymph-gland of an untreated male mouse taken in a similar manner to those shown in *Figs.* 152, 153. L, Lymph-gland; VM, Vestigial mamma. No mammary vestiges are present outside the circle. (× 12.)

The effects of œstrogenic compounds upon the mammæ of male mice, as seen in microscopical sections, may be considered under the following headings:—

1. Proliferation of ducts (gynæcomastia)
2. Dilatation of ducts } Cystic mastopathy
3. Hyperplasia of duct epithelium } Cystic mastopathy
4. Leucocytic infiltration
5. Increase of periductal fibrous tissue
6. Alveolar formations (adenomata?)
7. Cancer

1. Proliferation of Ducts or Gynæcomastia.—Sections of 29 mammæ taken from 23 adult male mice of various ages which had not been treated with benzene or any œstrogenic compound, revealed the presence of mammary ducts

in 5 only, and in these but a few cross-sections of ducts were seen (*Table II*). In 57 mammæ from male mice which had received applications of benzene only to the skin for prolonged periods, mammary ducts were seen in 12, and in 4 of these more than ten cross-sections of ducts were counted. In every instance the ducts were vestigial in character (*Fig.* 155). In 97 mammæ taken from male mice which

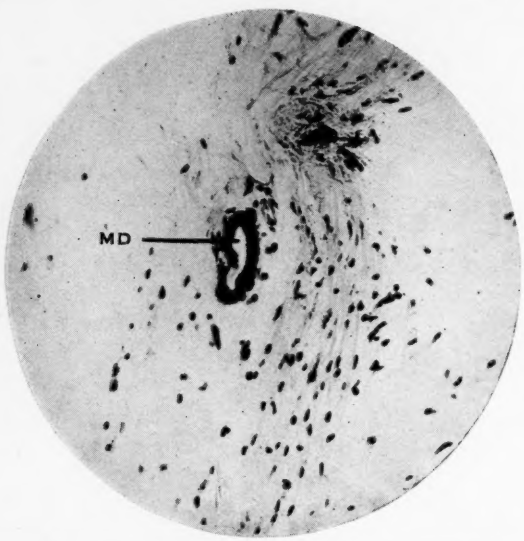


FIG. 155.—Section through duct (MD), of vestigial mamma of untreated male mouse. (× 180.)

had been treated with œstrin for a period of more than fifty days, ducts were visible in 62, and in 56 of these more than ten ducts could be seen in single sections. In 77 mammæ from male mice treated with œstrogenic compounds other than

Table II.—PROLIFERATION OF MAMMARY DUCTS IN MALE MICE FOLLOWING TREATMENT WITH ŒSTROGENS FOR MORE THAN FIFTY DAYS

TREATMENT	NUMBER OF MAMMÆ EXAMINED	NUMBER SHOWING DUCTS	PERCENTAGE	NUMBER SHOWING MORE THAN 10 DUCTS IN A SECTION (GYNÆCOMASTIA)	PERCENTAGE
Controls. No drugs applied	29	5	17·2	0	0
Benzene only ..	57	12	21·0	4	7·0
Œstrin in benzene	97	62	63·9	56	57·2
Other œstrogens ..	77	36	46·7	25	32·4

œstrin, mammary ducts were found in 36, with evidence of their proliferation in 25 (*Table II*). My intention had been to count the ducts shown in the different series of sections for comparison, but this was found impracticable owing to the great number of ducts present in some of the mice which had been treated with

œstrogenic compounds. However, an estimate of numerical value has been obtained by separating cases into two categories according to whether more than ten or less than ten ducts are visible in a single microscopical specimen. In making these records only those particular sections which showed the maximum number of ducts were used. Thus, in a series of sections made from an untreated male mouse the majority might show no mammary tissue at all, a single duct appearing in but a few sections; such a case would be recorded as positive in *Table II.* In the same way, if some preparations displayed only five or seven ducts, for example, while others from the same mamma showed more than ten, the record was based on the latter.

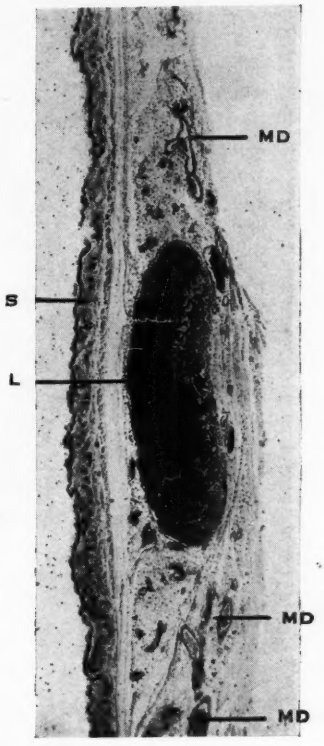
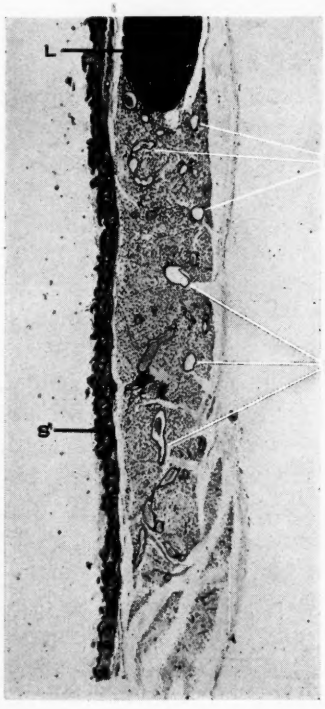


FIG. 156.—Mamma of a male mouse treated with œstrin for 190 days. Illustrates gynæcomastia. S, Skin; L, Lymph-gland; MD, Dilated mammary ducts. (× 12.)

Seeing that more than ten ducts were rarely seen in sections of mammæ taken from male mice which had not been treated with any œstrogenic compound, whereas sections taken in a similar manner from untreated female mice nearly always showed more than ten ducts, it seems justifiable to apply the term 'gynæcomastia' to the proliferation of ducts induced by œstrogenic substances in the mammæ of male mice, and revealed by this numerical criterion.

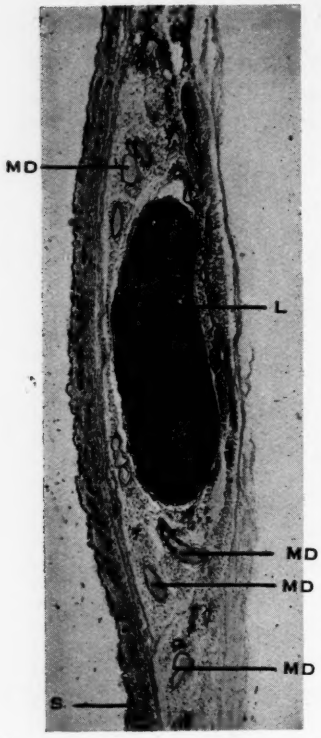


Another justification for using the term 'gynæcomastia' in the present circumstances is the apparent correspondence, within limits, between the changes induced by œstrin in the mamma of mice and pathological lesions of a comparable nature which occur in man.

2. Dilatation of the Ducts.—This was never seen in untreated male mice. In those which had been subjected to œstrin, dilated ducts were present in 52 mammæ out of a total of 58 in which mammary ducts could be demonstrated (*Figs.* 156–158). The cystic dilatations are filled with a material which stains pink with eosin and appears homogeneous. The cysts themselves seem to be formed,

FIG. 157.—Mamma of male mouse treated with œstrin for 245 days. Shows gynæcomastia. S, Skin; L, Lymph-gland; MD, Dilated mammary ducts. (× 12.)

in part at least, through a general increase in the length and diameter of a duct causing tortuosity and perhaps kinking.



The ducts may be lined by a cuboidal or columnar epithelium (*Fig.* 159) or by flattened epithelium (*Fig.* 160). These illustrations exemplify the fact that the type of epithelium does not depend upon the degree of tension within the duct. In *Fig.* 160 the duct appears flaccid, though lined by a flattened epithelium, whereas in the well-distended duct of *Fig.* 159 the epithelium varies from cuboidal to columnar.

FIG. 158.—Mamma of a male mouse treated with œstrin since birth (279 days). Illustrates cystic mastopathy. S, Skin; L, Lymph-gland; MD, Dilated mammary ducts. Hyperplasia of duct epithelium is present, though not distinguishable under this magnification. (× 12.)

In untreated unmated adult female mice, very wide differences are to be seen both as regards the number of mammary ducts present and their calibre. Such differences depend to some extent upon the stage of the œstrous cycle at which the mouse was killed. During œstrus the mammary ducts in mice become dilated, and, normally, return to their former thread-like dimensions during metœstrus (Cole). But this contraction is not always complete, and dilated ducts often

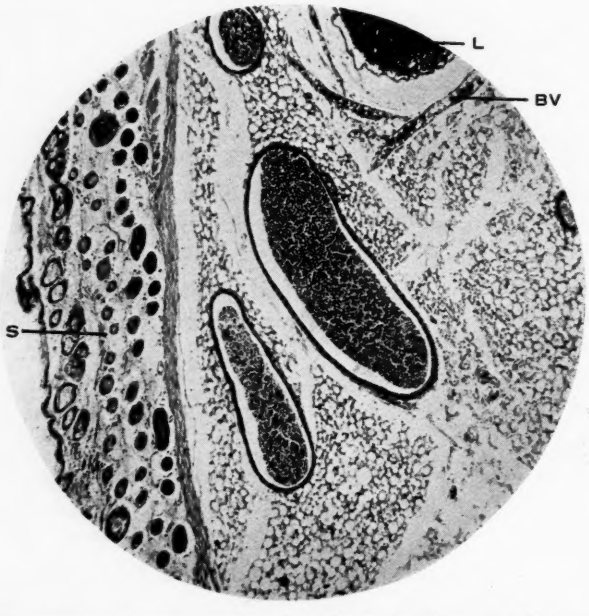


FIG. 159.—Mamma of male mouse treated with œstrin for 133 days. S, Skin; L, Iliac lymph-gland; BV, Blood-vessel. Three dilated ducts are shown. They are lined by a single layer of cells, varying from cuboidal to columnar, and are filled with material staining pink with eosin. Note absence of peri-ductal fibrosis or inflammatory reaction. (× 56.)

may be found in untreated female mice at all stages of the œstrous cycle. Among elderly unmated and untreated female mice great contrasts exist. In one the mammæ may be represented by a few non-dilated ducts resembling in their form the vestigial ducts seen in the untreated male, while in another the ducts are numerous, more dilated, and show here and there varying degrees of epithelial hyperplasia.

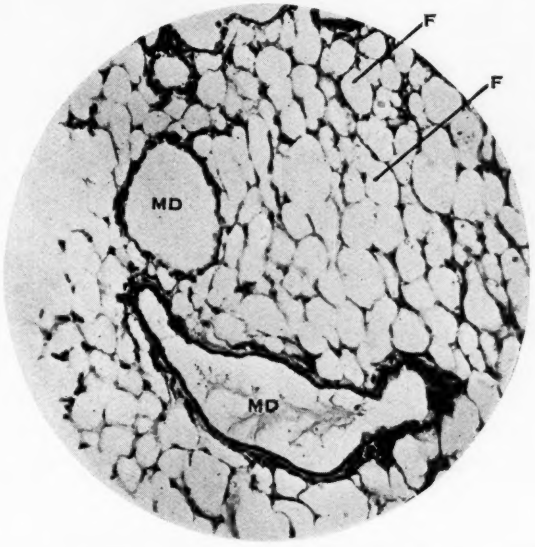


FIG. 160.—Mamma of male mouse treated with œstrin for 245 days. F, Fat cells; MD, Mammary ducts. Note: (*a*) Flaccid appearance of ducts; (*b*) Flattened epithelium lining the duct; (*c*) Absence of periductal fibrosis and inflammatory reaction. (× 100.)

3. Hyperplasia of the Epithelium.—This, like dilatation of the ducts, was never seen in the mamma of an untreated male mouse, though present in 40 per cent of the animals which had been submitted to prolonged treatment with œstrin (*Figs.* 161–164). Epithelial hyperplasia was of less frequent occurrence than dilatation of the ducts, and ensued later in the course of treatment with œstrin. A diagnosis of cystic mastopathy has been made in the course of this investigation only when dilatation of ducts and epithelial hyperplasia have both been present. The two conditions do not appear to advance at an equal rate as the experiment proceeds, and on looking through a number of microscope specimens the impression is acquired that to some extent the two conditions may be in inverse relationship—that is to say, that epithelial hyperplasia seems more often pronounced in those specimens which show relatively little dilatation of the ducts, while in the presence of extensive dilatation of ducts there may be but little hyperplasia of the epithelium.

If a wider experience substantiates this observation, it may be necessary to modify somewhat our views of the prognostic significance in women of mammary cysts. They might be regarded as sinister as they indicate an excess of œstrogenic effect—an excess which, if it continues, is known to lead eventually to epithelial hyperplasia. This latter, representing as it does a more advanced stage in the pathological process, would give rise to a more acute apprehension of the supervention of cancer. Naturally, because more easily observed, the cysts have hitherto

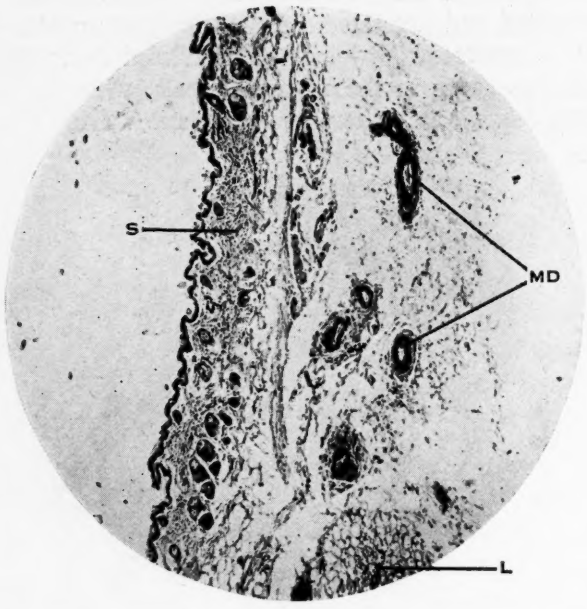


FIG. 161.—Mammary tissue of male mouse treated with œstrin for 142 days. Shows hyperplasia of epithelium of mammary ducts (MD) without dilatation. S, Skin; L, Lymph-gland. (× 56.)

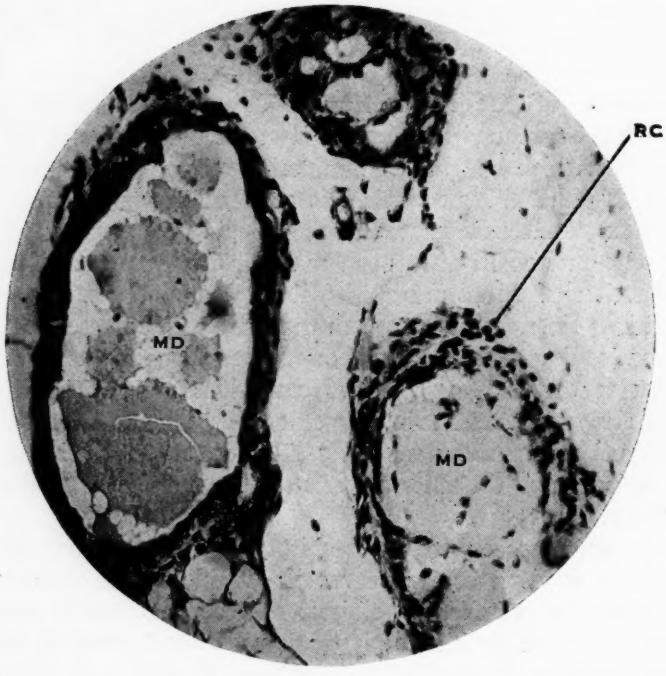


FIG. 162.—Mammary tissue of male mouse treated with œstrin for 154 days. Shows hyperplasia with dilatation of mammary ducts (MD). There is some round-cell infiltration (RC), and a few leucocytes are seen within the lumina of the ducts. (× 145.)

FIG. 163.—Section through two mammary ducts of a male mouse treated with œstrin for 144 days. Note: (*a*) Hyperplasia of epithelium with but little dilatation of duct; (*b*) Absence of periductal fibrosis; (*c*) Absence of inflammatory reaction. (× 400.)

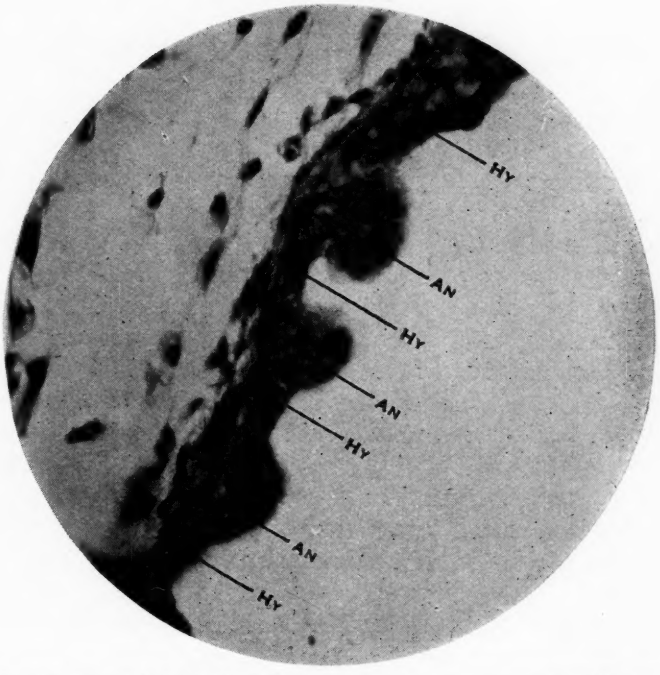


FIG. 164.—Section through wall of dilated mammary duct in a male mouse treated with ketomethoxy-œstrin for 337 days. Shows the partial replacement of hyperplastic cells (Hy) by anaplastic epithelium (An). (× 500.)

FIG. 165.—Section through mammary duct of a female mouse treated with ketomethoxyœstrin for 349 days. Shows the partial replacement of hyperplastic epithelium (Hy) by anaplastic epithelium (An). (× 500.)

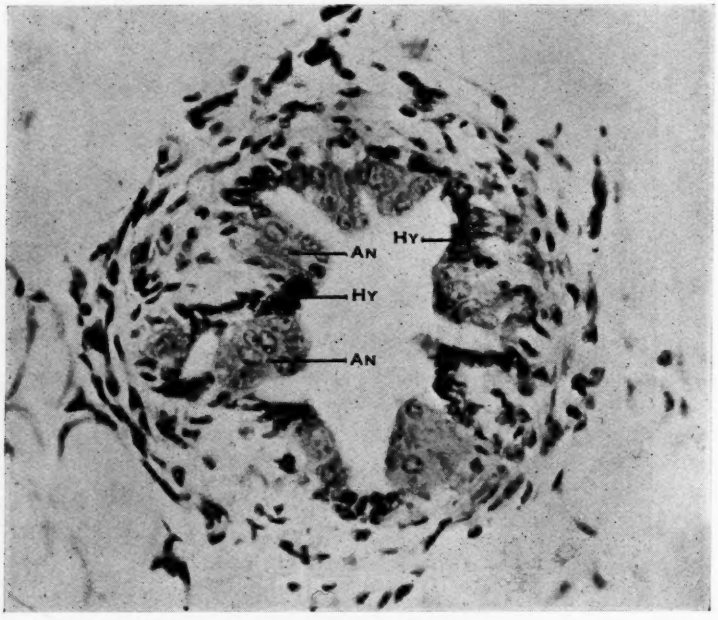


FIG. 166.—Section through mammary duct of a female mouse treated with œstrin for 429 days. Shows the partial replacement of hyperplastic epithelium (Hy) by anaplastic epithelium (An). (× 400.)

attracted too much attention, it would seem, in comparison with the more ominous hyperplasia, which has received, perhaps, too little. This is unfortunate, seeing that advanced hyperplasia may exist in one part of a breast with slight, if any, dilatation of the ducts, while in another part of the same breast there may be conspicuous cysts without overgrowth of the epithelium.

In our experimental work sections of mammæ have been regarded as showing epithelial hyperplasia when some of the ducts possess a lining more than one cell in thickness. In the earlier stages of this hyperplasia the cells have relatively little protoplasm and their nuclei stain darkly. After the applications of œstrin have been continued for a year or so a change may be seen not infrequently in certain areas of such hyperplastic epithelium (*Figs.* 164–166).

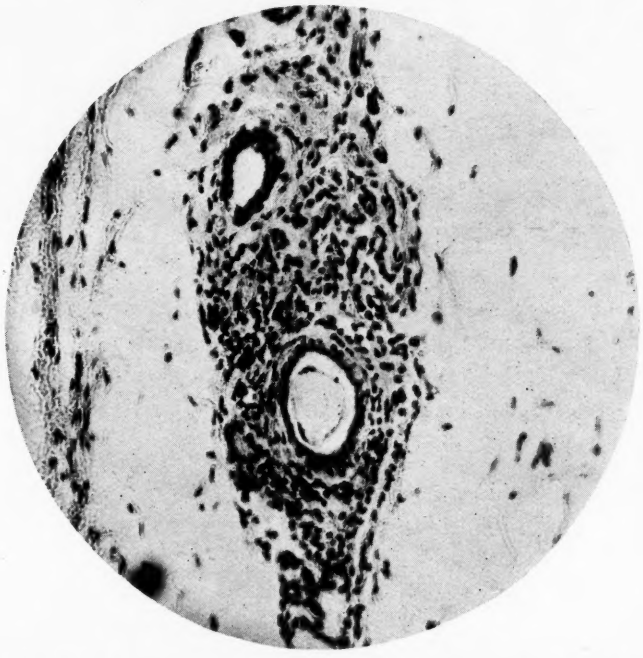


FIG. 167.—Section through two mammary ducts of a male mouse treated with œstrin for 234 days. There is copious round-cell infiltration. (× 180.)

The change consists in the appearance at various foci of larger cells, containing faintly staining cytoplasm with large, pale, vesicular nuclei and large nucleoli. These anaplastic-looking cells multiply and form small masses which replace the pre-existing type of epithelial cell.

4. Leucocytic Infiltration.—Leucocytic infiltration around the ducts is occasionally seen (*Figs.* 162, 167). The majority of the invading cells have the appearance of lymphocytes. As the condition is largely a matter of degree and may affect some of the ducts only, while others in the same microscopical section may be free, the relative frequency of leucocytic infiltration has not been expressed in numerical terms.

5. Increase in Periductal Fibrous Tissue.—Regarding the frequency with which an increase of the connective-tissue stroma surrounding the mammary ducts may occur under the influence of œstrin, it is also difficult to speak with

confidence. There is little tendency in the mouse, as compared with man, toward the formation of fibrous tissue, and I should prefer to leave as an open

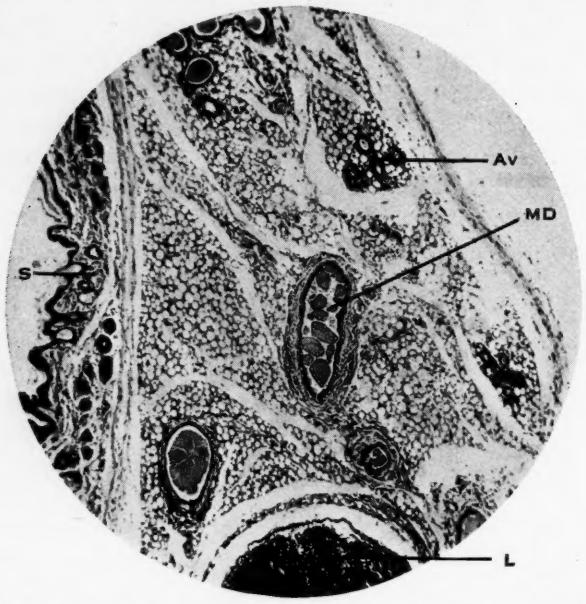


FIG. 168.—Mamma of castrated male mouse treated with œstrin for 411 days. S, Skin; L, Lymphatic gland; MD, Mammary duct; Av, Alveolar formation (? adenoma). Note: (*a*) Periductal fibrosis; (*b*) Hyperplasia of duct epithelium. (× 56.)

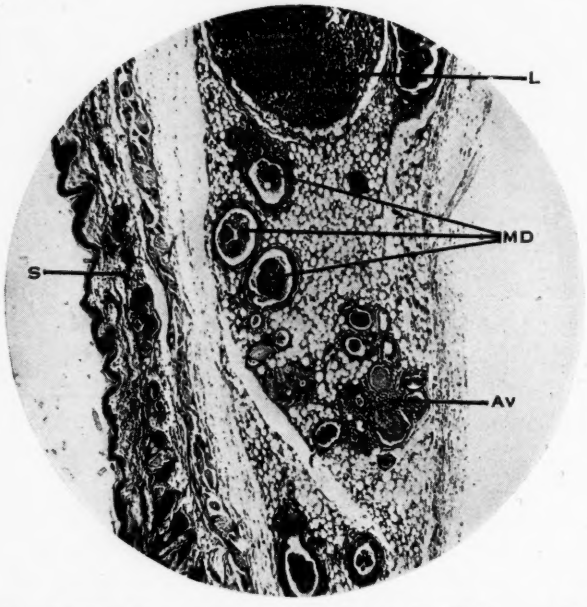


FIG. 169.—Mamma of castrated male mouse treated with œstrin for 419 days. S, Skin; L, Lymphatic gland; MD, Mammary ducts; Av, Alveolar formation (adenoma ?). Periductal fibrosis and epithelial hyperplasia are present. (× 56.)

question the frequency with which an increase of the periductal stroma may take place as a consequence of the administration of œstrin to mice. Occasionally

the increase of periductal fibrous tissue is considerable and easy to recognize (*Figs.* 168, 169).

Before discussing the development of tumours, a few words may be said about the distribution of the foregoing changes effected in the mamma by œstrin. The treatment of mice with œstrogenic compounds does not appear to affect the whole of a mamma in an equal degree. A similar observation has been made in connection with the effects of œstrogens on the prostate (Burrows). Even where obvious changes are present throughout all the mammary tissue visible in a single section, the nature of the lesions often varies in character and degree in different microscopic fields, or even in different parts of the same field. Dilatation may be more pronounced in one group of ducts than in another; epithelial hyperplasia may be advanced in one group of ducts whether cystic or not, and absent from another in the same section.

So it is with leucocytic infiltration, which seems quite capricious in its appearance. The suggestion has been made (Goormaghtigh and Amerlinck) that both hyperplasia and leucocytic infiltration may be determined to some extent by the presence or absence of retained secretion. Such a suggestion is not supported by the material which I have had the opportunity of examining.

Hyperplasia and leucocytic infiltration may be pronounced in ducts which are not dilated and do not appear to contain any secretion, and may be totally absent from cysts filled with secretion. Moreover, hyperplasia may be unaccompanied by any striking degree of leucocytic invasion, and the latter may occur in the absence of any marked condition of hyperplasia.

The foregoing observations have been made almost entirely on male mice. Female mice have not been introduced very much into the discussion because there is not such a clear distinction to be seen in the mammæ of females between those treated with œstrogen and untreated controls. Observations, however, have been made on female mice, and no essential difference has been found between the results of the persistent administration of œstrin to male and female mice respectively.

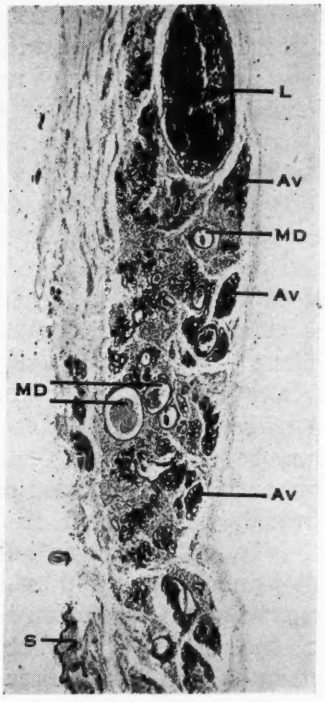


FIG. 170.—Advanced degree of gynæcomastia and cystic mastopathy induced in male mouse by applications of equilin for a period of 246 days. S, Skin; L, Lymph-gland; MD, Dilated mammary ducts (cysts); Av, Alveolar formations (adenomata?). (× 12.)

6. Benign Adenoma.—As already mentioned, the distribution in the breast of the changes induced by œstrin may be irregular, some parts of a gland showing perhaps advanced changes while other parts appear almost unaffected. This irregularity may result in the development of local collections of proliferated ducts which might conceivably be regarded as adenomata. And when the treatment with œstrogen has been prolonged, groups of alveolar formations also sometimes appear here and there (*Figs.* 168–170). Whether these alveolar formations, which in some specimens are profusely scattered through the mamma (*Fig.* 170) after

prolonged œstrogenic treatment, can be properly termed adenomata or not it is difficult to decide. A substantial development of fibrous tissue does not commonly happen in mice, and I have not seen in these animals any bulky, well-defined, and almost completely encapsulated fibro-adenomata comparable with those innocent tumours which occur in women and also in rats and dogs. If, however, these local collections of proliferated ducts and alveolar formations in the mouse are to be described correctly as adenomata, it is worth remarking that they appear to react to œstrin in the same manner as the rest of the mammary tissue. Therefore it appears reasonable to suppose that, equally with other parts of the breast, they might ultimately become the seat of cancer, without necessarily being peculiarly liable to this change. (*See* ADDENDUM I.)

7. **Mammary Cancer.**—This has been an uncommon development among the mice in our own experiments. With the males there has been but 1 example among 116 individuals treated with various œstrogenic compounds. (*See* ADDENDUM II.)

The infrequency of mammary cancer in our mice after the regular and prolonged administration of œstrin is in contrast with Lacassagne's results which I have mentioned earlier. But Lacassagne found that in the males of one of the strains of mice which he used no mammary tumours were induced by œstrin. The paucity of malignant growths among our male mice might therefore be explained, perhaps, by a natural refractoriness. Mice belonging to a recognized and pure strain have not been available for our own experiments. We have used stock mice, all purchased from the same dealer, and spontaneous cancer of the mamma among the females of this stock appears to be an uncommon occurrence. There may be other than familial causes for the infrequency of cancer in our treated males, but the further consideration of this matter involves too much hypothesis and too little ascertained fact to be profitable. Whatever the explanation may be, it does appear established that in certain strains of mice, if not in all, the prolonged administration of œstrin leads to an increased liability of the animal so treated, whether male or female, to suffer from cancer of the breast.

To say that œstrin induces cancer of the mamma in mice would, I think, not be justifiable in the present state of our knowledge. Possibly the part played by œstrin in this connection is to put the mamma in such a condition that it is liable to become the seat of cancer, which is rather a different proposition from the assertion that œstrin induces carcinoma. The administration of œstrin to mice in sufficient amounts over a long enough period is, as our experiments have shown, frequently followed by cystic mastopathy. And reasons can be advanced for regarding this condition as a preparatory stage toward cancer—that is to say, as a precancerous state.

DISCUSSION

An association between cystic mastopathy and mammary cancer in women has been thought to exist by some clinicians and pathologists for more than half a century. Sir Henry Butlin used to teach thirty years ago that chronic mastitis, as the condition used to be called, with or without the presence of obvious cysts, is probably by far the most common predisposing condition in cancer of the breast; and in a generation earlier a similar opinion was held by Sir James Paget.

At the present day there are varying views as to the frequency with which mammary cancer is preceded by, or associated with, chronic cystic mastopathy.

Some (Cappell) will place their association as recognizable in nearly 100 per cent of all cases of cancer of the breast, while yet others (Campbell) believe that the incidence of cancer following chronic cystic mastopathy is no higher than in breasts which were previously normal. The difference of opinion between those who do and those who do not hold that cystic mastopathy is a precancerous state is perhaps, as Campbell has recently suggested, largely the result of the different bases for their conclusions, the former being guided by histological inquiry and the latter mainly by clinical experience.

As remarked already, the more serious feature of cystic mastopathy from the prognostic standpoint appears to be, not the presence of cysts, but the presence of epithelial hyperplasia. The only sure way of recognizing the presence of cystic mastopathy, when the dilatation of the mammary ducts is insufficient to cause the presence of cysts large enough to be appreciated by palpation or to be seen with the naked eye, is by the examination of microscopical sections. Therefore it would seen advisable to discard all opinions as to its frequency as a forerunner or accompaniment of mammary cancer which depend upon clinical impressions only.

Largely through the teaching of Sir Lenthal Cheatle and his colleagues it has become generally admitted now that the old term 'chronic cystic mastitis' is a misnomer, the condition not being essentially of an inflammatory nature. For this reason the term 'cystic mastopathy' has been used in this paper, although, possibly, a more explicit and better one might be 'œstrogenic mastopathy'.

In our experiments dilatation of the mammary ducts was never observed in male mice except in those which had been treated by a compound known to be œstrogenic. On the other hand, dilatation of mammary ducts was found in 59 per cent of male mice which had been treated with bi-weekly applications of œstrin over a period of fifty days or longer, and was usually accompanied by some degree of epithelial hyperplasia. In other words, cystic mastopathy was never seen in the males apart from treatment with œstrogens, whereas it was commonly present in those which had been treated with œstrin, and was often present following the administration of certain other compounds closely allied to œstrin.

The collective experience of those who have investigated the influence of the ovaries or of œstrin itself upon the mammæ of mice seems to show that cancer of the breast also is, in part at least, dependent upon this influence.

When the problem of human mammary cancer is considered in the light of the facts set out in this paper, it would seem that a temporary dilatation of the mammary ducts in a woman prior to the menopause might be regarded as a purely physiological condition. A persistent dilatation of the ducts, if such a condition were detected, would, however, give rise to some anxiety at whatever age it occurred. It would be presumptive evidence of an abnormal production of œstrogen, or an exaggerated responsiveness to its influence on the part of the mamma, or a diminution of the natural antagonism to œstrogenic action in that individual. If such a persistent dilatation were accompanied by hyperplasia of the epithelium, a more advanced stage of the over-reaction to œstrin would be recognized, and the anxiety as to the likelihood of cancer appearing in the future would be increased correspondingly.

Accepting œstrogens as the cause of cystic mastopathy, and this as a common precursor of cancer, how, it may be asked, could this knowledge be applied for the prevention or treatment of cancer of the breast in women? To-day the reply

would be that it is well to understand the pathological causes and processes of any disease, and also to diagnose abnormal conditions in the mamma at the earliest stage possible, and particularly before the morbid state has progressed beyond recall.

There does not appear to be any insurmountable obstacle to the recognition in an individual of an abnormal production or retention of œstrogen; the amount present at different times in the blood and urine is capable of fairly accurate assay. On the other hand, once the necessity for such tests is appreciated, it can hardly be doubted that means will be found for ascertaining also what may be described as the susceptibility of any individual to the influence of œstrin. Thus the rate of disappearance of œstrin injected into the blood-stream already can be ascertained by experiment, and such an investigation might throw light on the cause of excessive reactivity to the influence of œstrin.

Natural antagonisms, both to the production of œstrin and to its action, exist in the body—antagonisms which can be recognized in the regulation of the œstrous cycle. For example, progestin, the hormone, or one of the hormones, derived from the corpus luteum, is in several respects an opponent in the living organism to the activities of œstrin. It seems not impossible that such natural agencies, when their characters are better understood, and the active substances themselves are more easily obtainable, might be utilized to adjust the balance, the aberration from which appears to be the cause of cystic mastopathy. Many of the effects of œstrin are reversible, and tissues which have undergone changes under its temporary influence return rapidly to their former state after the effective supply of œstrin has been withheld. This reversibility seems to reveal therapeutic possibilities, in spite of the fact that dilatation of the mammary ducts may persist for a considerable time after œstrin has been withheld. That mammary cysts do not speedily disappear after the supply of œstrin has been stopped does not, however, lessen the importance of an early diagnosis in women of the conditions which lead to cystic mastopathy, nor does it destroy every hope of providing a remedy. Success in such endeavours, it may be thought, would bring cystic mastopathy into the list of preventable diseases. And if, as many have supposed, cystic mastopathy is in fact a frequent precursor of cancer, it may be justifiable to hope that its early recognition and cure will render cancer of the breast to some, and perhaps to a large, extent an avoidable condition.

So far as concerns the cure of an established mammary cancer, experimental investigation of the action of the ovaries and of œstrin has brought to light no material for an increase of optimism. It has shown that ovariotomy, if performed early in life, may prevent cancer of the breast in mice; unfortunately it has also shown that little or no such preventive action follows an ovariotomy late in life, even though it be done prior to the appearance of any mammary tumour. That is to say, if the ovaries have exercised their function of producing œstrin over a sufficient length of time before their removal, cancer of the breast will not be prevented by ovariotomy. Nor will removal of the ovaries materially affect the course of a mammary cancer already present.

Many surgeons will remember the brief wave of optimism with which ovariotomy was regarded thirty years ago by a few enthusiasts as a treatment for inoperable carcinoma of the breast. Sir George Beatson, who introduced the procedure, was led to it by a recognition of the relationship between the mamma and the ovary. He did not regard the operation as a cure, but thought that,

combined with the administration of thyroid gland, it had a favourable influence on the local condition in the mamma itself. He stated clearly that visceral metastatic deposits were not influenced by the treatment. Some of his followers, however, were not so judicious, and for a short while there were surgeons who believed the operation to have some curative value.

Before concluding this paper reference may be made to the mammary changes which have occurred as sequels to the prolonged administration to male mice of œstrogens other than œstrin. It would be premature to discuss these results in detail because the work is not sufficiently advanced; they are summarized in *Table III*, and show, at least, that several of these compounds will induce pathological changes in the mamma of the mouse.

Table III.—Effects on the Mammæ of Male Mice of Administering Various Œstrogens, other than Œstrin, for Prolonged Periods (Fifty Days or More)

Œstrogen	Source	Solvent and Concentration	Number of Mammæ Examined	Number with Gynæcomastia	Number with Cystic Mastopathy	Cancer
Ketomethoxyœstrin	Girard Cook	Benzene 0·1 %	29	11	13	0
Dihydroxyœstrin (Dimenformon)	Organon Laboratories	Alcohol 0·1	5	0	0	0
Trihydroxyœstrin (Theelol)	Parke, Davis & Co.	Alcohol 0·1	4	3	3	0
Equilenin	Girard	Benzene 0·1	5	1	1	0
Equilin	Girard	Benzene 0·1	10	2	0	0
9 : 10–Dihydroxy–9 : 10–di–*n*–propyl–9 : 10–dihydro–1 : 2 : 5 : 6–dibenzanthracene ..	Lawson*	Benzene 0·3	15	8	5	0
9 : 10–Dihydroxy–9 : 10–di–*n*–butyl–9 : 10–dihydro–1 : 2 : 5 : 6–dibenzanthracene ..	Cook†	Benzene 0·3	9	0	0	0

*Cook, J. W., Dodds, E. C., Hewett, C. L., and Lawson, W., *Proc. Roy. Soc.*, 1934, cxiv, 272.
† Cook, J. W., *Jour. Chem. Soc.*, 1931, 489.

SUMMARY

1. The earliest pathological effect of œstrin observed in the mammæ of male mice is a proliferation of the mammary ducts, that is to say, *gynæcomastia*. This proliferation of ducts is occasionally accompanied, especially when the treatment has been prolonged, by the formation of what look like clusters of acini.

2. Speedily following the proliferation of ducts is their dilatation, with the formation of *mammary cysts*.

3. The next stage is that of hyperplasia of the epithelium lining the ducts, sometimes accompanied by an increase of the periductal stroma. This stage of hyperplasia combined with the presence of cysts, represents the '*chronic cystic mastitis*' of the old, and the '*cystic mastopathy*' of the new terminology. In view of its causation it might perhaps better be termed 'œstrogenic mastopathy'. In advanced cases epithelial *anaplasia* may be seen in the ducts.

All these foregoing changes are produced by œstrin, in the same sequence, in both male and female mice.

4. The proliferative and other effects of œstrin on the mamma are often distributed in different degrees throughout the gland, and a pronounced local proliferation perhaps may be in the mouse the equivalent of a *benign adenoma* in a woman.

5. In some of the mice treated with œstrin, whether male or female, *carcinoma* of the breast is apt to develop. Lacassagne states that this development in any individual mouse appears to depend in part at least upon that individual's responsiveness to œstrin. This responsiveness in mice, he states, may be an inherited character. It is a measurable quality and varies greatly among different pure-bred strains.

6. In women the output of œstrogens and the rapidity of their disappearance from the blood-stream can be estimated. Other factors which determine an individual's responsiveness to œstrogens can hardly be regarded as beyond the scope of future pathological inquiry.

7. Accepting these premises, it would appear possible to ascertain in some measure the liability of any individual woman to suffer from cystic mastopathy and from cancer of the breast before such conditions had actually developed. In other words it would be possible to anticipate the much desired early diagnosis of cancer of the breast by the recognition of a state in which cancer, though not yet present, is likely at some time or other to arise.

8. There is reason to expect that any divergence from a normal physiological equilibrium between the output of œstrogens and their antagonists may prove adjustable by artificial means.

9. If these conclusions are supported by experience, it will be possible to regard cancer of the breast to some extent as a preventable disease.

ADDENDA

ADDENDUM I.—Further study of the action of different œstrogens has shown that the mamma does not respond in the same way to every œstrogen used. Œstrin, for example, readily causes proliferation and dilatation of the ducts, but has little tendency to induce the development of alveoli. Equilin, on the other hand, has little if any tendency to cause proliferation and dilatation of the ducts, but apparently assists in the formation of alveoli. These differences in action between the various known œstrogenic compounds are at present being investigated.

ADDENDUM II.—Since this paper was written another male mouse of the series has developed mammary cancer. Of 125 male mice treated with repeated applications of œstrin and surviving for 100 days or more, 2 have now shown mammary cancer. Twenty-six of the total number of mice had been castrated prior to the administration of œstrin, and both instances of mammary cancer have occurred in this group of castrated mice.

I should like to mention with gratitude our debt to Dr. Girard, without whose generosity a large part of this inquiry could hardly have been carried out. He has presented us with considerable amounts of œstrin, equilin, and equilenin which had been prepared by himself in a pure crystalline state. We also have to thank the Organon Laboratories and Messrs. Parke, Davis and Company for supplying us with samples of dihydroxyœstrin and trihydroxyœstrin. It is a pleasure to mention these several kindnesses, and also to acknowledge the valued co-operation of my colleagues at this Institute, and my special indebtedness to Professor J. W. Cook. The microscopical sections and the photographic reproductions are the work of our technicians, Messrs. W. Davis and E. W. Woollard.

REFERENCES

BEATSON, SIR G. T., "The Treatment of Operable and Inoperable Carcinoma of the Mamma", *Trans. Med.-Chir. Soc. Glasgow*, 1910, ix, 166.

BURROWS, H., "Pathological Conditions induced by Œstrogenic Compounds in the Coagulating Gland and Prostate of the Mouse", *Amer. Jour. Cancer*, 1935, xxiii, 490.

BUTENANDT, A., "Untersuchungen über das weibliche Sexualhormon. Darstellung und Eigenschaften des kristallisierten 'Progynons'", *Deut. med. Woch.*, 1929, lv, 2171.

BUTLIN, H. T., "On Predisposing and Precancerous Conditions of the Breast", *Clinical Jour.*, 1904, xxiii, 337.

CAMPBELL, O. J., "The Relationship between Cystic Disease of the Breast and Carcinoma", *Arch. of Surg.*, 1934, xxviii, 1001.

CAPPELL, D. F., "Observations on Cancer of the Breast in the Light of Experimental Cancer Research", *Glasgow Med. Jour.*, 1931, cxv, 181.

CHEATLE, SIR G. L., and CUTLER, MAX, *Tumours of the Breast*, 1931. London.

COLE, H. A., "The Mammary Gland of the Mouse, during the Œstrous Cycle, Pregnancy, and Lactation", *Proc. Roy. Soc.*, 1933, B, cxiv, 136.

CORI, C. F., "The Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinomas of Mice", *Jour. Exper. Med.*, 1927, xlv, 983.

DOISY, E. A., VELER, C. D., and THAYER, S., "The Preparation of the Crystalline Ovarian Hormone from the Urine of Pregnant Women", *Jour. Biol. Chem.*, 1930, lxxxvi, 499.

GESCHICKTER, C. F., LEWIS, D., and HARTMAN, C. G., "Tumors of the Breast Related to the Estrin Hormone", *Amer. Jour. Cancer*, 1934, xxi, 828.

GOORMAGHTIGH, N., and AMERLINCK, A., "Réalisation expérimentale de la Maladie de Reclus de la Mamelle chez la Souris", *Bull. du Cancer*, 1930, xix, 527.

HALBAN, J., "Die innere Secretion von Ovarium und Placenta und ihre Bedeutung für die Function der Milchdrüse", *Arch. f. Gynäkol.*, 1905, lxxv, 353.

HARDE, E., "Influence des Hormones et des Vitamines dans la Production des Adéno-carcinomes mammaires chez la Souris", *Comptes rend. Soc. de Biol.*, 1934, cxvi, 999.

LACASSAGNE, A., "Apparition de Cancers de la Mamelle chez la Souris male, soumise à des Injections de Folliculine", *Comptes rend. Acad.*, 1932, cxcv, 630.

LACASSAGNE, A., and NYKA, W., "Apropos d'une Pathogénie de l'Adéno-carcinome mammaire: Recherche de la Folliculine dans la Colostrum", *Comptes rend. Soc. de Biol.*, 1934, cxvi, 844.

LATHROP, A. E. C., and LOEB, L., "On the Part played by Internal Secretion in the Spontaneous Development of Tumours", *Jour. of Cancer Res.*, 1916, i, 1.

LEWIS, D., and GESCHICKTER, C. F., "Estrin in High Concentration yielded by a Fibro-adenoma of the Breast", *Jour. Amer. Med. Assoc.*, 1934, ciii, 1212.

LOEB, L., "Internal Secretion as a Factor in the Origin of Tumours", *Jour. of Med. Res.*, 1919, xl, 477.

MURRAY, W. S., "Ovarian Secretion and Tumour Incidence", *Jour. of Cancer Res.*, 1928, xii, 18.

PAGET, SIR J., "On Indurations of the Breast becoming Cancerous", *St. Bart's. Hosp. Rep.*, 1878, 65.

THE INNERVATION AND MUSCULAR ACTIVITIES OF THE DISTAL COLON: WITH A NOTE ON THE SURGICAL TREATMENT OF CONSTIPATION*

By HUGH C. TRUMBLE

SURGEON TO OUT-PATIENTS, ALFRED HOSPITAL; SURGEON TO AUSTIN HOSPITAL, MELBOURNE

In common with other parts of the alimentary canal, the distal colon is capable of peristaltic contractions. In this region, however, peristalsis seems to be kept in abeyance for long periods, so that waste material may accumulate and be stored until it becomes convenient to evacuate the fæcal mass. Holzknecht[1] pointed out that the progressive slowing of the rate of the onward passage of the contents of the gut, which is to be noted from the duodenum to the rectum, is not due to a corresponding weakening or slowing of the rate of peristalsis, but to an increase in the length of the intervals between movements. Thus, whilst in man peristaltic movements may be observed frequently in the jejunum, the colon is practically always at rest, only three or four powerful movements of brief duration occurring in twenty-four hours. In the rectum movements are still more infrequent. It is obvious that delays are of service to the animal, in that time is afforded for the completion of digestion and absorption in the small intestine and proximal colon, whilst the storage of fæces which takes place in the distal colon is a distinct convenience. This storage results in the accumulation of a large amount of material for the evacuation of which a special neuromuscular apparatus has been evolved. When this apparatus is brought into action, mass evacuation or defæcation results.

It is proposed to consider here some aspects of the specialized functions of storage of fæces and defæcation, to record certain physiological and clinical observations, and finally, to discuss briefly the surgical treatment of constipation. Peristalsis will not be considered in detail, but for the purpose of this paper it is of importance to note that in animals, at any rate, peristaltic waves continue to propel the contents of the gut after all of the extrinsic nerves have been severed and allowed to degenerate, and that such a state of affairs appears to be compatible with quite good function of the alimentary canal (Langley and Magnus[2]). Peristalsis appears to be a neuromuscular phenomenon involving a nervous reflex subserved by the intrinsic nerve plexuses of the gut. That peristalsis may be controlled by way of the extrinsic nerves will appear later.

THE EXTRINSIC NERVES OF THE DISTAL COLON

By 'distal' colon is meant that portion which normally contains formed fæces and is emptied during defæcation (Elliott and Barclay-Smith[3]). In carnivora this includes most of the colon, in man that portion between the region of the splenic flexure and the anus.

---

* From the Baker Medical Research Institute.

Nomenclature.—It is proposed to use the nomenclature adopted by Langley and Anderson.[4]

Anatomy.—The plan of the autonomic nervous outflows to the colon in cats, rabbits, and dogs was discussed in detail by Langley and Anderson in another paper.[5] A description of the outflows, as seen in various animals and man, is given by the author in a separate paper.[6] For the convenience of the reader, diagrams showing the plan on which the nerves concerned are laid down in the dog and in man are included here (*Figs.* 171, 172).

The distal colon receives nerve-fibres from the lumbar cord (upper set—Langley) and from the sacral cord (lower set). The segments giving origin to the

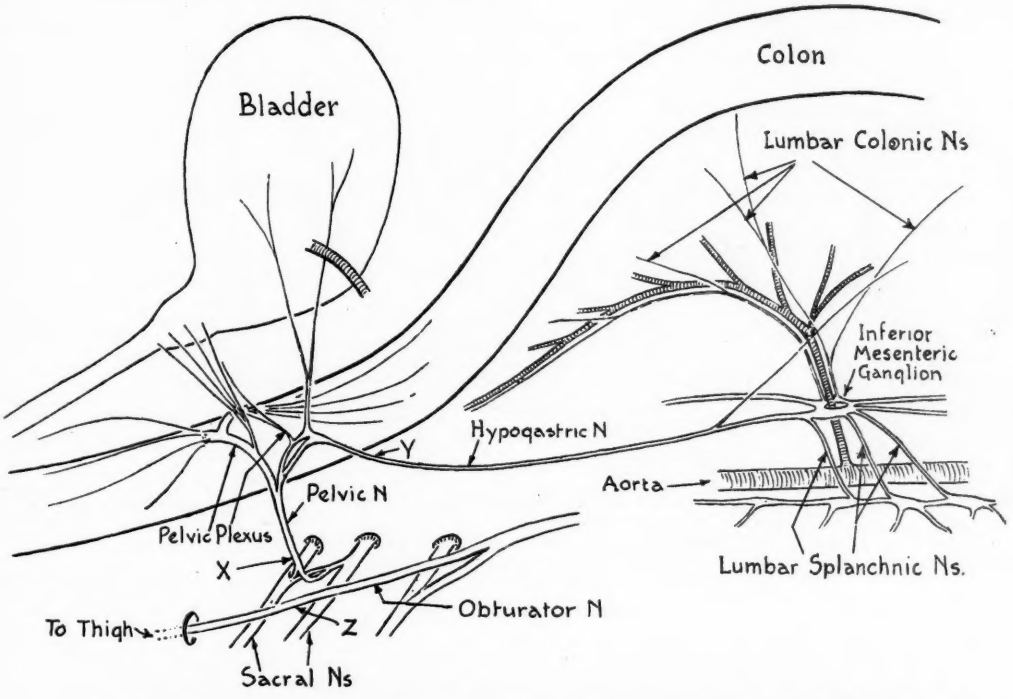


FIG. 171.—Diagrammatic representation of the nerves in the lumbar and sacral outflows of the autonomic nervous system in the dog. The inferior or lumbar splanchnic nerves pass from the lumbar trunks forwards and downwards to the region of the inferior mesenteric ganglia. A contribution from the cœliac ganglion also joins the ganglionic ring, which encircles the inferior mesenteric artery, and contains several small ganglia. From the ring arise numerous nerves which pass to the colon, and the two hypogastric nerves, which pass into the pelvis to enter the pelvic plexuses. From certain of the sacral nerves (mainly the second) twigs arise which join to form the pelvic nerves, one on each side of the body. The pelvic nerves pass into the pelvic plexuses. From these numerous nerves pass to the pelvic viscera.

lower-limb plexus intervene between the two sets. Langley showed that in animals the two groups of visceral nerves and the limb plexus arise commonly from certain definite segments of the spinal cord, but that variations are frequently to be observed. He described the usual arrangement as median, whilst pre-fixed and post-fixed plexuses were designated anterior and posterior respectively. Thus in rabbits with an anterior arrangement the main sympathetic effect on the colon was seen on stimulating the third and fourth lumbar nerves, whilst in the posterior type the effect was best on stimulating the fourth and fifth lumbar nerves.

As regards the physiological plan on which the nerves are laid down, it is

assumed that the reader is familiar with the general features of the autonomic nervous system as described by Gaskell and Langley. *Fig.* 173 will serve to illustrate some of the chief reflex arcs in the portion of the system under consideration. On the afferent side (receptor neurones of Gaskell) the fibres of both the lumbar and sacral outflows pass from the viscera by way of the posterior spinal roots to the spinal cord. From cells in the grey matter of the lumbar cord arise axones which pass by way of the ventral roots, lumbar nerves, white rami, sympathetic trunks, and inferior splanchnic nerves, to end by arborizing about cells in the inferior mesenteric ganglia situated further afield in the hypogastric nerves or pelvic plexuses. These fibres, which were designated by Gaskell as 'connector', by

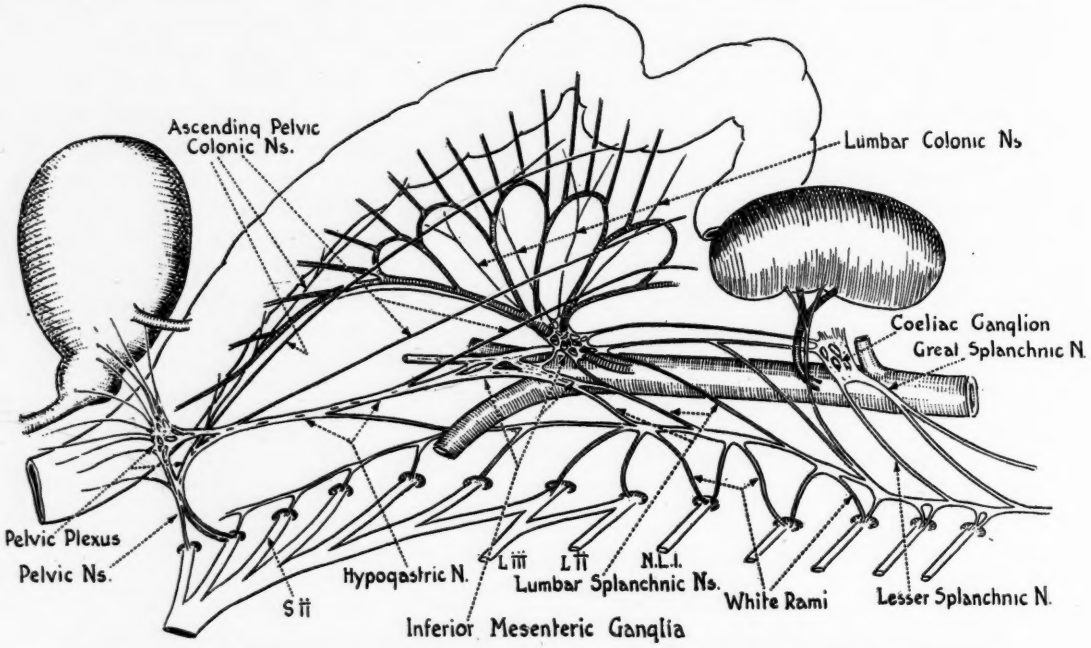


FIG. 172.—Diagrammatic representation of the nerves of the lumbar and sacral outflows of the autonomic nervous system in man. Note the striking resemblance in general plan to that in the dog as depicted in *Fig.* 171. The inferior mesenteric 'ganglion' is again not discrete but is rather a ganglionated network pierced by the inferior mesenteric artery. From the network numerous nerves pass to the colon and rectum. The pelvic nerves arise mainly from the third and fourth sacral nerves and join the hypogastric nerves to form the pelvic plexuses. The pelvic colonic nerves radiate as shown to reach that part of the colon supplied by the inferior mesenteric artery. Some of the uppermost nerves run for a time in company with the hypogastric nerves, as described recently by Telford and Stopford. The colon and the kidney are reflected ventrally.

Langley as 'pre-ganglionic', fibres, may divide and send branches to more than one ganglion cell, and some of these branches may cross the mid-line to reach ganglia of the opposite side of the body. From cells in the grey matter of the sacral segments of the spinal cord fibres arise which pass by way of the sacral ventral roots, sacral nerves, and pelvic nerves through the pelvic plexuses to end by arborizing about nerve-cells situated on, or in, the walls of the pelvic viscera. Thus the cell stations of this outflow are further removed from the central nervous system than in the case of the lumbar outflow. As a general rule the afferent fibres, constituting the receptor elements of the reflex arcs, and the connector or pre-ganglionic fibres are medullated, whilst the effector or post-ganglionic fibres are non-medullated. There are, however, exceptions to this rule.

It is reasonably certain that centres exist at higher levels in the central nervous system which exert a controlling influence on the arcs just described. These higher connections will not be considered in this paper.

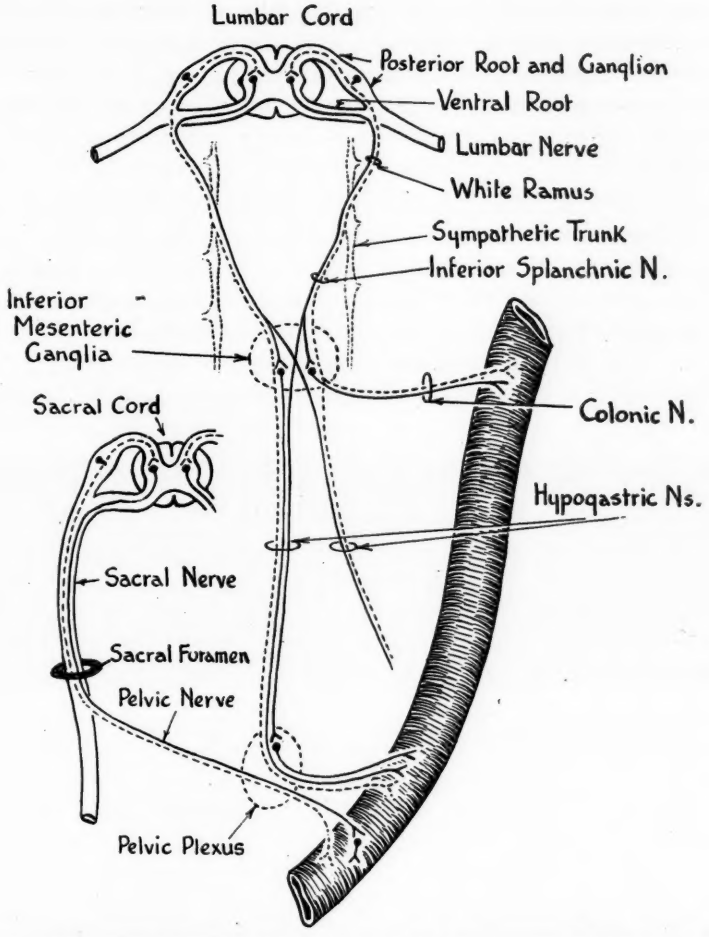


FIG. 173.—Diagrammatic representation of some of the more important reflex arcs in the lumbar and sacral outflows of the autonomic nervous system. Afferent or receptor fibres are represented by interrupted lines. Their cell bodies are situated in the posterior root ganglia. Pre-ganglionic or connector fibres have their cells in the lateral horns of the grey matter of the spinal cord, and their fibres pass out to link up with cells situated as shown. The cells of the post-ganglionic or effector neurones of the lumbar outflow are situated in the inferior mesenteric ganglia or ganglia of the pelvic plexuses, whilst those of the effector neurones of the sacral set are situated in the plexuses on or in the wall of the colon. (For further description *see* text.)

PHYSIOLOGICAL ACTION OF THE EXTRINSIC NERVES OF THE DISTAL COLON

THE LUMBAR NERVES

In the course of many experiments on dogs the author has frequently stimulated the inferior splanchnic nerves and branches of the inferior mesenteric ganglion, without ever obtaining other than inhibitory effects upon the colon. The sphincter ani was not observed. Langley[4] noted occasional motor effects upon the colon on stimulation of the nerves of the lumbar outflow in rabbits and cats. Other

writers have described motor effects in dogs. On the other hand, section of the inferior splanchnic nerves has sometimes, but not always, been followed immediately by an astonishing increase of tone, the colon hardening and shortening quite forcibly, very occasionally showing also a series of peristaltic waves. It was pointed out by Bayliss and Starling[7] that there was difficulty in demonstrating any activity of the gut whilst its thoraco-lumbar nerve-supply was intact; and also that stimulation of any sensory nerve served to inhibit the gut, if the splanchnic nerves and spinal cord were unharmed. Surgeons practically never see true peristalsis in human beings when operating in the abdomen except in patients under high spinal anæsthesia.

Apparently the gut is reflexly inhibited when the abdomen is opened, and at least one limb of the arc runs in the splanchnic nerves (thoracic, in the case of the small gut; lumbar, in the case of the colon). Section of the inferior splanchnic nerves or the corresponding white rami, or of the distal branches of the inferior mesenteric ganglion, releases the colon from reflex inhibition. Spinal anæsthesia acts similarly. The author has frequently observed an immediate 'release' in dogs following upon section of the inferior splanchnic nerves. This 'release'

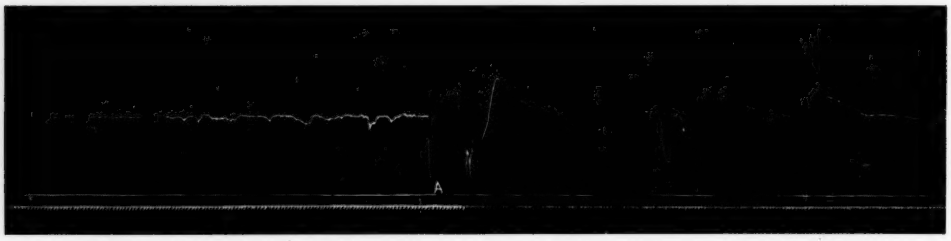


FIG. 174.—Enterographic record of the contractions of the circular muscle coat of the distal colon in a macaque monkey, showing the 'release phenomenon'. The animal was anæsthetized and immersed in a bath of warm Ringer's solution. For a period of about twenty minutes prior to the point marked A, the colon was inert and caused very little movement of the recording lever. At the point A the inferior mesenteric ganglionated network was crushed. Almost immediately the colon became very active, and a series of peristaltic waves starting near the hepatic flexure passed downwards. Contraction of the circular muscle at the site of attachment of the enterograph caused a downward movement of the recording lever. A decrease in tone followed each peristaltic wave. The time-marker records periods of five seconds.

is indicated by a rapid increase in tone of both coats and increased response to stimulation applied locally to the gut or through the medium of the pelvic nerve. The most dramatic immediate 'release' observed occurred, however, in a macaque monkey. In *Fig.* 174 is seen an enterographic record of contractions of the circular coat of the distal colon. The animal was anæsthetized (ether) and the abdomen opened, after which it was immersed in a bath of warm Ringer's solution. The colon was moderately distended throughout its length. An enterograph was attached transversely to the descending colon about 8 in. from the anus. For about twenty minutes the gut was exceedingly inert and the recording lever showed very little movement. The fibres of the nerve network in the region of the inferior mesenteric ganglion were then crushed. Almost immediately peristaltic waves originating near the hepatic flexure began to pass down the colon to the anus. Fæces were passed freely. The tracing shows well a series of powerful waves. It is worth noting that they are not preceded, but followed, by loss of tone of the circular coat.

Twice, in human beings, after section of the inferior splanchnic nerves for the relief of desperate constipation, the author has observed a similar but less dramatic release phenomenon. In each case the colon, which was distended and inert, became, after the nerve section, much more tonic, ringed in appearance, and readily responsive to pinching. As will be detailed later, certain forms of constipation appear to be permanently cured by the above procedure. In other words, the 'release' observed immediately after section of the inferior mesenteric nerves is not merely a passing phenomenon.

The Pelvic Nerves

Elliott and Barclay-Smith,[3] after experimenting upon a wide range of animals, came to the conclusion that stimulation of the pelvic nerve caused contraction of both coats of the distal colon and rectum, the contraction of the longitudinal coat and recto-coccygeus following rapidly on stimulation and causing the gut to shorten and descend towards the pelvis, whilst the contraction of the circular coat was delayed, so that perhaps fifteen to twenty seconds after the commencement of stimulation a wave appeared at the upper end of the distal colon and then slowly passed down the gut to the anus.

Bayliss and Starling,[8] after experimenting on dogs and rabbits, stated that stimulation of the pelvic nerves (after destruction of the thoraco-lumbar outflow to the colon) caused rapid simultaneous contraction of both coats of the whole colon or any part thereof.

Langley and Anderson[5] experimented on cats, rabbits, and dogs. They found that stimulation of the pelvic nerves always caused contraction of the longitudinal coat and recto-coccygeus, whilst in the rabbit there was a delayed variable contraction of the circular coat, sometimes peristaltic in nature, sometimes spastic. In cats the circular effect was less marked, and in dogs there was only occasionally a belated peristaltic wave, which the observers thought might be accidental.

In view of the dissimilarity of the results obtained by the above observers, the author has carried out numerous investigations in dogs. Morphia has been administered as a routine procedure (1 to 1½ gr.) and followed by light ether anæsthesia. After opening the abdomen and exposing the nerves, the animals were usually placed in a bath of Ringer's solution, kept at about 37·5° C. The solution often became polluted by blood or dust from the animal's coat, even after preliminary washing, or by fæces passed during the experiment, so that, later, resort was had to the following technique. After making a long mid-line incision from sternum to pubis, the abdominal muscles were detached from the pelvic girdle by cutting their insertions close to the bone. This could be done practically bloodlessly. A piece of string was then passed through the lower end of each rectus muscle and served to retract these widely, and so to form a kind of parapet on each side of the abdomen, which banked up enough Ringer's solution to cover the gut. Access to the pelvis was greatly facilitated and trouble from contractions of the muscles of the belly wall almost eliminated. Warm Ringer's solution was poured freely into the trough so formed in the animal's abdomen throughout the experiment, and thus the liquid bathing the coils of gut was kept constantly fresh and clear.

Hooded electrodes were placed on the pelvic nerves, one or both as was convenient. In order to eliminate undesirable reflex effects, various procedures

were adopted at different times. Sometimes stimulation was applied with all nerves intact, sometimes after division of the inferior splanchnic nerves or hypogastric nerves. On many occasions the pelvic nerves were severed at their points of emergence from the sacral nerves. In a few cases the brain and spinal cord were entirely destroyed after tying the carotid and vertebral arteries in the neck. After this procedure artificial respiration was resorted to and anæsthesia discontinued. In all cases a weak faradic current easily appreciable by the tip of the tongue was used to stimulate the nerves. Sometimes the effect on the colon was observed but not recorded; more often one or two enterographs were attached at different levels and a graphic record was obtained.

Certain effects were obtained quite constantly, irrespective of the state of preservation of the spinal cord, brain, or lumbar splanchnic nerves. One half of the bladder always went immediately into powerful spasm when the corresponding nerve was stimulated. Almost as rapidly and constantly the colon and rectum shortened and were drawn down towards the pelvis, there being no obvious

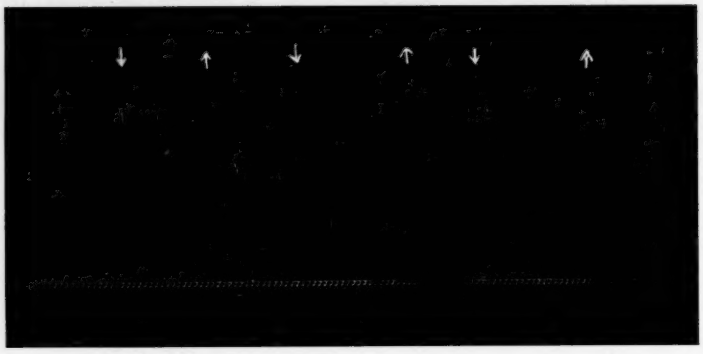


FIG. 175.—Enterographic record of the contractions of the circular muscle coat of a dog's colon, showing an 'Elliott' response. Under ether anæsthesia the carotid and vertebral arteries were tied and the brain was destroyed. Artificial respiration was commenced. The abdomen was opened, the central connections of the inferior mesenteric ganglion were divided, and an electrode was placed on the left pelvic nerve. The enterograph was attached just above the middle of the colon. The down-pointing arrows indicate the commencement, the up-pointing arrows the cessation, of faradic stimulation of the left pelvic nerve. Each stimulus was followed after an interval by a peristaltic wave commencing high up in the colon and passing down the gut. The time signal records periods of five seconds.

evidence of a unilateral effect. Up to this point the results were similar to those recorded by the above-mentioned observers. Upon the circular coat there was no constancy of effect. Often nothing more than a slight increase in amplitude of the pendulum beats, as shown on the tracing, was observed. In a few cases stimulation of one pelvic nerve was followed almost immediately by a spastic contraction of the circular coat, always best marked in the lower colon, but spreading sometimes well up towards the proximal third. This effect is similar to that described by Bayliss and Starling, but it was not often obtained. Much more frequently an 'Elliott response' was seen. The usual rapid shortening and descent of the colon was constantly observed, then after an interval of from ten to thirty seconds a wave appeared high up in the colon and slowly passed down the gut, frequently driving fæces before it. In *Fig.* 175 is seen a record of waves following stimulation of the left pelvic nerve in a dog after destruction of the brain and decentralization of the inferior mesenteric ganglion. The enterograph

was attached slightly above the mid-point of the colon so that the delay on the tracing between the stimulation and response does not represent the true latent period but includes also the time taken by the wave to pass from its point of origin down to the enterograph. In *Fig.* 176 the response is much more prompt. The enterograph was attached higher up on the colon than in the previous case, but

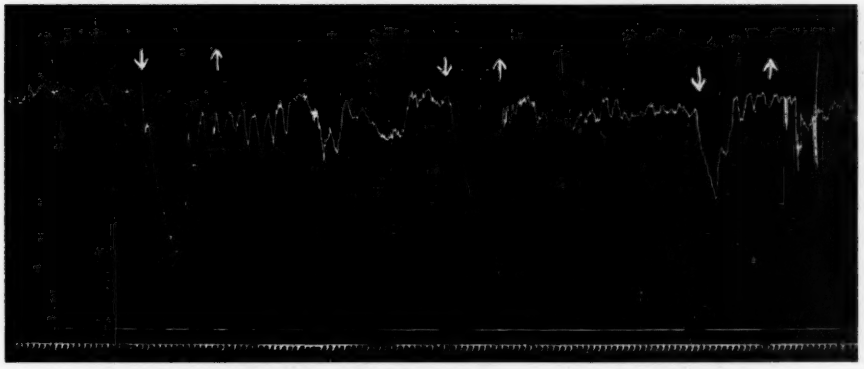


FIG. 176.—Enterographic record of the contractions of the circular muscle coat of a dog's colon, showing a more immediate response than in *Fig.* 175. The conditions of the experiment were the same as those detailed in the legend of *Fig.* 175, except that in this case the right pelvic nerve was stimulated and the enterograph was attached a little higher on the colon. Stimulation of the right pelvic nerve was followed almost immediately by the appearance of a peristaltic wave in the proximal third of the colon. This wave passed down the gut. Time = five seconds.

even so the effect is much more rapid than usual, and is very similar to that shown in *Fig.* 177, which is a record of the contractions of the longitudinal coat of the lower colon in the same dog obtained later in the experiment than *Fig.* 176. The

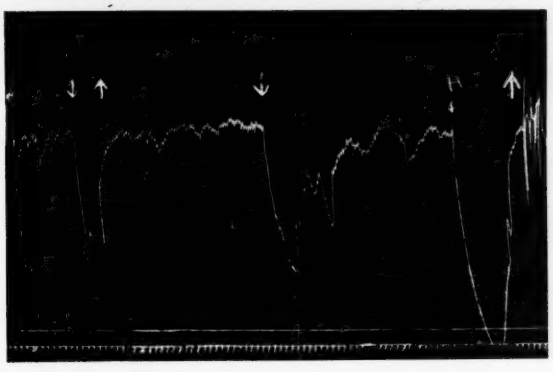


FIG. 177.—Enterographic record of the contractions of the longitudinal muscle coat of a dog's colon (distal segment). This record was obtained from the same animal as was that shown in *Fig.* 176, but later in the experiment. Stimulation of the right pelvic nerve was followed almost at once by a powerful contraction of the longitudinal coat and descent of the colon towards the pelvis. Arrows indicate commencement and cessation of faradic stimulation. The second stimulation evoked strong contraction of the longitudinal muscle coat which passed off although stimulation was continued. At the point marked H the current increased in strength. Another powerful contraction followed. Time = five seconds.

response is not of the 'Bayliss-Starling' type, because the contraction appeared high up and spread down the colon.

In some of the experiments, after a delay following stimulation a series of waves passing downwards from near the ileocolic junction has been observed.

Fig. 178 is a tracing recorded by two enterographs; one (lower tracing) attached to the colon in its upper third, the other (upper tracing) in its middle third. Following stimulation there is a slight immediate effect on the upper tracing due to contraction of the longitudinal muscle, then after a considerable delay a powerful peristaltic wave at the upper enterograph (lower tracing), which reached the lower enterograph (upper tracing) after an interval. Then follow a series of waves passing from above down and affecting the lower enterograph (upper tracing) later than the upper. Sometimes the waves faded away before reaching the lower enterograph. *Fig.* 179 shows a second series of waves after the gut between the enterographs had been incised from the antimesenteric border so as to divide more than half of the tube. As will be seen, the waves had no difficulty in passing over the point of hemisection, although the contents of the gut exuded through the gaping wound. This observation is of interest in that it demonstrates that a distension of the gut in advance of a peristaltic wave is not necessary for the continuance of the latter.

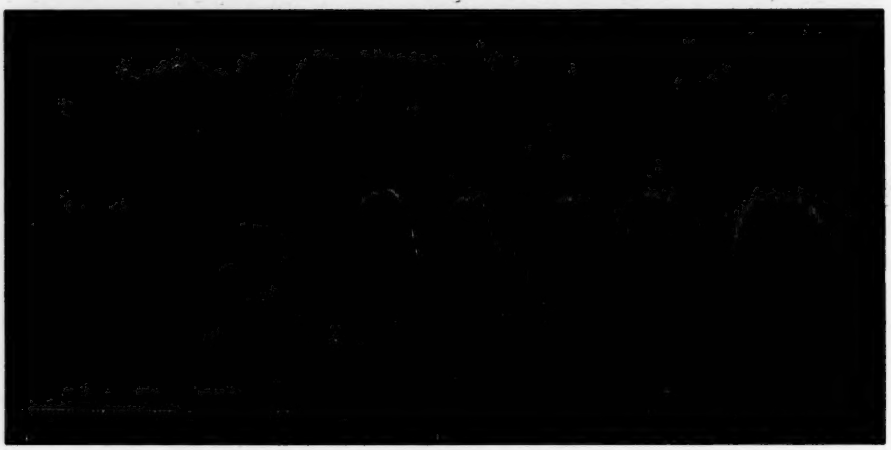


FIG. 178.—Enterographic records of contractions of the circular muscle coat of a dog's colon. Under general anæsthesia all four cerebral arteries were ligated in the neck and the brain was destroyed, after which artificial respiration was instituted. The abdomen was opened, the central connections of the inferior mesenteric ganglion were divided, and an electrode was placed on the right pelvic nerve. Two enterographs were attached to the colon, the upper on the gut recording below on the tracing. At the point L prolonged faradic stimulation of the right pelvic nerve was followed by a series of powerful waves passing downwards over the colon and recorded by both enterographs in turn. Some of the waves failed to reach the lower enterograph (upper tracing). Time = five seconds

On the whole the author's results are similar to those obtained by Elliott and Barclay-Smith. Langley did not immerse his animals in a saline bath, which may explain why he did not obtain a better response from the circular coat on stimulation of the pelvic nerves. The immediate contraction of the circular coat, noted by Bayliss and Starling, is sometimes, but not often, seen. Regarded from the standpoint of defæcation, the Elliott type of response would seem to be ideal. The author has not yet been able to discover why in one case one response is observed and in another a different effect. It remains to note that a true 'Elliott' type of response has been obtained in dogs at different times after destruction of the brain and spinal cord, division of the pelvic nerves, hypogastric nerves, and the central connections of the inferior mesenteric ganglion. It would seem, therefore, that the impulse imparted to the pelvic nerve by experimental stimulation

is transmitted by fibres of the pelvic nerve direct to the neuromuscular mechanism of the colon and not by way of the spinal cord or hypogastric nerves.

The Effect on the Colon of Section of the Pelvic Nerves.—Elliott[9] noted that after section of both pelvic nerves in cats, fæcal retention did not ensue; on the contrary, fæces were passed more frequently than usual. On the other hand, in rats after destruction of the lower part of the spinal cord, fæces accumulated in the colon, and he looked upon the gut as being paralysed.

Merzbacher[10] divided the sensory roots of the lumbar and sacral nerves in dogs, and observed that the animals no longer defæcated after the manner of dogs, co-ordinated movements of the tail, legs, and so on being absent. Fæces accumulated in the rectum without evoking strong contractions, and sometimes even protruded passively from the anus without exciting the sphincter to activity. Pellets of fæcal material would sometimes fall out whilst the animals were eating.

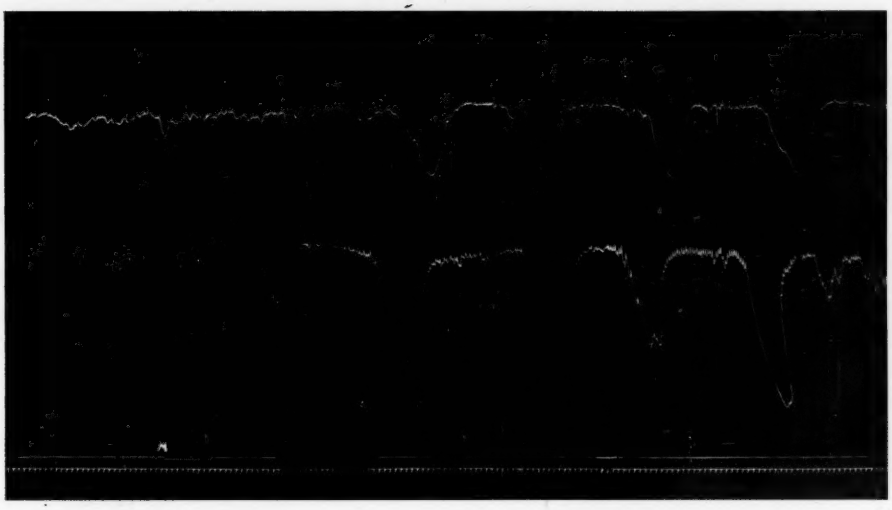


FIG. 179.—Records from the same animal as that from which *Fig.* 178 was obtained, but later in the experiment, after an incision had been made into the gut more than half dividing it, the wound being left gaping so that fæcal material forced down from above exuded through it, and did not pass into the segment of gut below the incision. Stimulation of the right pelvic nerve (point M) was followed as before by the passage down the gut of a series of waves, which passed over the wounded area and were recorded by both enterographs. The upper tracing is from the segment of gut below the incision. Time = five seconds.

In the previous experiments, destruction of the spinal cord or roots of the lumbo-sacral nerves, or division of the pelvic nerves, involved much more than the pelvic nerve-supply to the colon. The author has endeavoured to eliminate such troubles as paralysis of skeletal muscles and the bladder by dividing the colonic branches of the pelvic plexus. This procedure, of course, results in the division of some fibres from the hypogastric nerves which run in company with the branches of the pelvic nerve to the colon and rectum.

Technique.—A small lower mid-line incision is made, and the abdomen is opened. The rectum is drawn upwards, and it is then possible to see several small branches from the pelvic plexus on each side ascending to enter the colonic wall and lying on its antero-lateral aspects just under the reflexion of the peritoneum. The latter is cut through with scissors, the visible nerves are divided,

together with small vessels accompanying them, and then a forefinger is introduced and the rectum is stripped away from the structures lying in front of and lateral to it, until the pelvic floor is reached. The stripping must be thorough.

This operation has been performed successfully in eleven dogs, and in all the after-history has been much as follows. After a few days, during which defæcation is usually much deranged, the animals begin to pass several small fæcal masses each day. Defæcation in normal dogs usually results in the extrusion of a fairly large amount of fæcal material, made up of an elongated mass often followed by one or more small oval nodules. This may be described as a mass evacuation, and occurs once, twice, or three times daily. In the experimental animals of this series, the comparatively infrequent mass evacuations were not seen, but, on the contrary, fæces were passed in the form of oval lumps, one at a time, frequently throughout the day and night. Only very occasionally was a mass passed at all comparable with that evacuated by normal dogs. During defæcation the animals squatted in the usual way, and behaved as though there

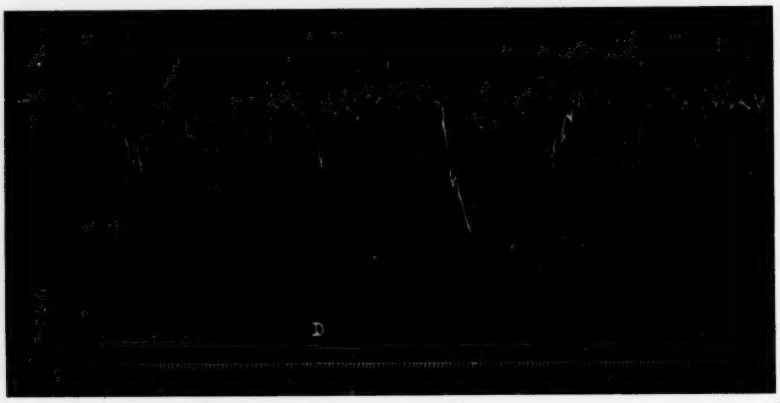


FIG. 180.—Enterographic record of the contractions of the circular muscle coat of a dog's colon. The colonic branches from the pelvic plexus were divided on Jan. 28, 1931. On Feb. 11 the animal was anæsthetized. The carotid and vertebral arteries were tied and the brain and spinal cord destroyed. Artificial respiration was instituted. The abdomen was opened and an enterograph attached to the colon in its proximal third, after which the animal was immersed in a bath of warm Ringer's solution. Spontaneous peristaltic waves passed at irregular intervals down the colon and fæcal material was passed. The tracing shows a series of waves following on a period of inactivity. At D the lumbar splanchnic nerves were stimulated, following which peristalsis was temporarily inhibited. Time = five seconds.

were nothing abnormal. The dogs were observed for periods of up to nine months' duration. One dog became ill (distemper) one month after operation, and died. The colon was contracted and completely empty as though it had been washed. A second dog became ill two weeks after operation. Under anæsthesia the brain and spinal cord were destroyed, and the abdomen was opened. Powerful spontaneous peristaltic waves were seen passing down the colon, and soft-formed fæces were passed into the bath. *Fig.* 180 is a tracing of the colonic movements in this animal, showing a series of spontaneous peristaltic waves. At the point D the inferior splanchnic nerves were stimulated, causing inhibition of peristalsis for a brief period.

Another dog was kept for nine months, apparently in perfect health except for the frequent passage of small fæcal masses. Under general anæsthesia the abdomen was opened, and the colon seen to be of smaller calibre than normal

and of good tone. After division of the central connections of the inferior mesenteric ganglion stimulation of the pelvic nerves had no effect on the colon, though the bladder contracted as usual. No peristalsis was seen until hypertonic saline was injected into the gut, after which powerful waves appeared. In one dog kept alive for two months, it was observed at the second operation that section of the inferior splanchnic nerves was followed by great increase in tone amounting to spasm of the colon. Another dog, in which the inferior splanchnic nerves were divided at the same time as the pelvic colonic nerves, defæcated as described above. At the second operation five weeks after the first the bowel was very tonic in appearance.

It may be noted here that in one dog which was not kept alive after the experiment, stimulation of either pelvic gave a good 'Elliott response'. The visible colonic nerves from the pelvic plexus on one side were then severed, after which stimulation of the corresponding pelvic nerve had no effect on the colon, although the bladder contracted normally. The same result was then obtained on the other side. Further, in none of the dogs which were observed after degenerative section of the pelvic colonic nerves did stimulation of the pelvic nerves evoke any response in the colon, although the bladder contracted normally. These observations make it fairly certain that the pelvic nerve-supply to the colon was destroyed, at least in great part. It is possible that minor branches to the sphincter ani region may have escaped destruction.

It was pointed out above, that division of the pelvic colonic nerves destroyed the colonic fibres from the sacral outflow, probably completely, but also resulted in the destruction of fibres from the lumbar outflow passing to the colon by way of the hypogastric nerves and the pelvic plexuses. The effect described above is not due to the destruction of the lumbar supply to the rectum or sphincter ani internus, as division of the hypogastric nerves or lumbar splanchnic nerves is not followed by loss of storage and mass evacuation. Further, in a few instances, both pelvic nerves have been divided proximal to the pelvic plexuses, whilst the hypogastric nerves remained unharmed. After this the animals defæcated in much the same fashion as did those in which the mixed pelvic colonic nerves had been destroyed.

It seems to be quite certain that the pelvic nerve carries fibres which when stimulated cause the distal colon to evacuate its contents. In normal defæcation some stimulus affects the afferent limb of an arc of which the above-mentioned fibres form the connector (Gaskell) or pre-ganglionic (Langley) segment. This action of the pelvic nerves has long been recognized. Further, it appears that the normal effect on the colon is similar to that described by Elliott as occurring in animals and frequently obtained by the author. It also seems likely that the pelvic nerves subserve a second important function, which does not appear to have been recognized. By virtue of this function the distal colon is able to store fæcal material for a considerable time. Thus dogs normally pass a large elongated stool, together with one or two smaller masses, about two or three times a day. Evidently material brought down to the distal colon by numerous peristaltic waves has been held up and welded into one typical mass or more. Much the same process must take place in human beings. After degenerative section of the pelvic colonic fibres or pelvic nerves, dogs do not store fæces, but pass numerous small oval masses throughout the day and night. Storage and mass evacuation

are abolished, and the inherent peristaltic mechanism of the alimentary canal, previously kept under control by the pelvic nerves, comes to the fore and material is passed as it becomes available. Fæcal retention is never seen. It is possible that excessive activity of those fibres of the pelvic nerve which subserve the 'storage' function might cause constipation, but the author has no evidence to support such a view. On the other hand, it would appear that diminished activity, or even destruction of the pelvic nerves, should not cause constipation *per se*. It is to be noted that lesions of the spinal cord or cauda equina involve the nerve-supply to skeletal muscle and the bladder, so that constipation might follow as an indirect result of widespread paralysis and infection.

It is possible that the fibres in the pelvic nerves which control and inhibit peristalsis in the distal colon may be to some extent under voluntary control. It is common experience that the act of defæcation may be deferred voluntarily, and the presence of some nervous mechanism subserving this action must be assumed. That the final pathway lies in the pelvic nerves rather than in the lumbar splanchnic nerves is suggested by observations in human beings with lesions of the cauda equina. All voluntary control is lost; and once defæcation is started it cannot be checked. Further, destruction of the lumbar splanchnic nerves is not followed by loss of control, if the pelvic nerves remain intact.

It is also quite likely that the pelvic nerves contain similar fibres destined to reach the bladder musculature and to exert on it a control similar to that just described in respect of the colonic musculature.

That one set of nerves should contain fibres subserving two functions which are to some extent antagonistic is by no means unique. Langley and Anderson[4] noted that whilst the usual effect upon the colon of stimulation of the lumbar splanchnic nerves was inhibitory in nature, motor effects were frequently to be observed. Barrington[11] noted that in cats section of the pelvic nerves was usually followed by loss of tone of the bladder musculature, but that on some occasions there followed instead a persistent contraction of the muscle. Barrington suggests the possibility of the presence in the pelvic nerves of fibres which inhibit the bladder, although he considers this unlikely.

A view which is widely held is that certain individuals are 'vagotonic', others 'sympatheticotonic' by nature. It is unnecessary to discuss what is meant by these terms. With regard to the colon, it is commonly stated that the two sets of nerves, sacral and lumbar, antagonize one another, and that under certain circumstances one or other may gain the upper hand and so upset the harmonious working of the viscus. Thus the lumbar outflow has been destroyed for the relief of constipation, in order to leave the sacral nerves unopposed. The author would put it that the procedure results in release of the intrinsic neuromuscular mechanism from abnormal reflex interference. When both pelvic and lumbar nerves are destroyed the intrinsic mechanism gains unfettered control, and succeeds in evacuating the contents of the distal colon.

Clinical Observations.—It occurred to the author that in cauda equina lesions in man defæcation should be similar to that just described. With a lesion below the second lumbar vertebra the pelvic nerve-fibres would be destroyed, whilst the lumbar sympathetic outflow would remain intact. The bladder would be involved as well as the colon. The effect of such a lesion should be seen best in a patient who was not debilitated or bedridden as a result of paralysis of skeletal

and bladder musculature, bed-sores, and infection of the urinary tract. It is obviously essential that no doubt should exist as to the completeness of the interruption of the nerves in question. Curiously enough, a suitable case came under the author's notice almost immediately.

A man of 32, a railway employee, was injured in a train accident on June 10, 1929. A skiagram taken after a short interval showed that the spine had been completely severed through the disc between the third and fourth lumbar vertebræ, the two bodies appearing side by side on the negative. There could be no reasonable doubt that the nerves of the cauda equina had been completely severed as well. After the injury retention of urine necessitated catheterization, and on July 13, suprapubic drainage was instituted. A period followed during which infection of the urinary tract and bedsores were troublesome.

The man was admitted to the Austin Hospital, and in February, 1930, there were no reflexes present at the knees or below. Weak voluntary extension was present at the knee on the right side, whilst on the left side it was somewhat stronger, and fair flexion was also present. Sensation was absent on the right side from just above the knee, and on the left side from just below the knee. Automatic voiding of urine was noted in June, 1930, the suprapubic wound having healed.

When first seen by the author in June, 1931, the patient was in excellent health, getting about in a wheeled chair. There was evidently a complete severance of all nerves below the second lumbar on the right side and the third lumbar on the left side. It was reasonably certain that the parasympathetic nerve-supply to the bladder and rectum was destroyed, whilst probably the lumbar sympathetic supply to the same organs was intact, or only partly destroyed. The man was in excellent health, able to get about in a wheeled chair, and to exercise his legs to some extent. The abdominal muscles were normal. There was no gross infection of the urinary tract.

A careful study of the functioning of the bladder and rectum was begun. When the bladder was distended the patient had a sensation of fullness in the hypogastrium. If he neglected to void urine it was passed involuntarily. In order to prevent this, he had got into the habit of attempting to micturate every two hours. By straining he was usually able to do so, often passing as much as 10 oz. of urine. There was no sensation evoked in the urethra by the passage of urine, but the feeling of distension was relieved.

From the point of view of this paper, defæcation was of more interest. Usually the patient took two alophen pills daily. Salts or cascara caused loss of control. During periods of constipation the patient complained of stomach-ache, referred to the centre of the abdomen. When the bowel was about to void there was some sort of sensation. The act could not then be delayed voluntarily. Enemata did not cause any definite sensation. A finger in the rectum was scarcely felt. The anal sphincters were atonic and patulous. Whilst on occasions a whole day would pass without the passage of any fæcal material, it was usually quite otherwise. As stated above, the patient habitually attempted to micturate every two hours, and frequently whilst doing so he passed fæces. Defæcation occurred commonly about three times daily, sometimes more, sometimes less. Almost invariably two, three, or four small soft, discrete, oval lumps were passed at each attempt, never a large mass approximating to the normal stool.

To all intents and purposes defæcation in this case was similar to that recorded above as occurring in animals after section of the pelvic colonic nerves. Mass defæcation was lost, storage was lost, and small fæcal masses were passed at frequent intervals, apparently as a result of peristaltic action.

THE EFFECT UPON THE COLON OF EXCISION OF THE RECTUM

Radical excision of the rectum is almost certain to result in the destruction of the pelvic nerve-supply to that part of the distal colon which is left behind after operation (*see Fig.* 172). As a rule after this procedure patients defæcate through a sigmoid colostomy. Constipation does not follow, as might be expected by the

proponents of the theory of unbalanced nerve action. On the contrary, fæces are usually passed involuntarily several times daily, and at each action it appears that several small amounts are extruded seriatim, as though by separate peristaltic waves. This effect is probably due to the removal of the influence of those fibres of the pelvic nerves which subserve storage of fæces. Although many of the fibres of the lumbar outflow to the colon are still intact, peristalsis cannot be inhibited voluntarily.

Practical Applications.—Royle,[12] in a paper published in 1924, stated that certain of his patients were relieved of constipation as a result of ramisection performed primarily for the relief of spastic paralysis of the lower limbs. Wade[13] subsequently practised an operation in which he divided on the left side the white rami from the first and the second lumbar nerves, the visceral branches of the lumbar sympathetic chain, and the trunk itself at the pelvic brim, in the treatment of cases of Hirschsprung's disease, with encouraging results. Judd and Adson[14] removed the greater part of the lumbar trunks on the left or on both sides with good results. The author has discussed these operations and described that designed and practised by himself in another paper.[15]

Rankin and Learmonth[16] designed an operation very similar to that of the author, but somewhat more extensive in its scope. In the author's operation the majority of the inferior splanchnic nerves and the cœliac root of the inferior mesenteric ganglion are divided near the origin of the inferior mesenteric artery from the aorta. Rankin and Learmonth divide the 'presacral' nerve and, tracing this upwards, remove the whole of the network of nerves in the region of the base of the inferior mesenteric artery. In effect, he removes what the author has called the 'inferior mesenteric ganglionated network' (*see Fig.* 172).

In all these operations the lumbar sympathetic outflow to the lower abdominal viscera is destroyed in greater or less part. As a result of further experience, the author believes that in most cases simple resection of part of the hypogastric nerves (or the 'presacral nerve') is sufficient to obtain the desired effect. On occasions it is desirable to destroy the sympathetic supply to the lower limbs as well as that to the viscera, and this is done by a bilateral lumbar sympathectomy, performed through a paramedian abdominal incision.

Selection of Cases and Type of Operation.—Three main groups may be described:—

1. The first group comprises cases in which there is severe constipation associated with gross dilatation of the colon, and includes cases of Hirschsprung's disease. The operation should be radical, aiming at destruction of the greater part of the lumbar sympathetic supply to the colon. This is best attained by Learmonth's or the author's operation. The approach is through the abdomen and the attack is directed at the inferior mesenteric ganglionated network. The operation may be tedious in the presence of much adipose and lymph-glandular tissue. The results are usually good, but in some cases not permanent.

2. The second group comprises cases in which there is severe constipation associated with chilblains or 'chilblain circulation' of the extremities. Many of these patients are very miserable as a result of the state of their bowels and the extreme irritation of chilblains. Operation in such cases is designed to relieve both conditions. Both lumbar trunks below the first lumbar ganglion are excised, usually at one sitting, through a paramedian abdominal incision. The results are most gratifying, both as regards bowel function and the circulation of the lower limbs.

3. In the third group are placed those cases in which extreme constipation, which is unresponsive to conservative measures, is associated with other troubles such as dysmenorrhœa, neurasthenia, indigestion, and poor health generally. The colon is usually not dilated and may appear to be quite tonic. When other measures have failed, resection of portion of the hypogastric nerves may be tried. This is a fairly simple operation. Usually the bowel function is much improved and this reacts favourably on the patient, particularly upon his mental state. The gut appears to be released from some baneful reflex interference. Dysmenorrhœa, if present, is relieved.

It is hardly necessary to state that no patient should be subjected to operation until conservative measures have been thoroughly tried out and have failed. On the other hand, intractable constipation may make a person very miserable, and an operation holding out some hope of relief should not be denied him when all other measures fail to give relief.

SUMMARY AND CONCLUSIONS

In considering the normal functions of the distal colon it is pointed out that the muscle coats of this portion of the gut are capable of powerful peristaltic contractions. Peristalsis continues in the gut quite satisfactorily after all of the extrinsic nerves are divided and allowed to degenerate. In the distal colon peristaltic action is apparently controlled and kept in abeyance for long periods by a superimposed influence which is exerted through the medium of the pelvic nerves. Thus storage of fæces is rendered possible until such time as it is convenient to evacuate the bowel. Activity of the muscular coats of the distal colon may be inhibited also by artificial stimulation of the nerves of the lumbar outflow, and probably this inhibitory influence operates as a result of reflex stimulation in the intact animal. Further, it is probable that abnormal reflex activity may be at the root of certain forms of constipation. Division of the nerves in question should, and often does, remove the inhibitory influence and relieve constipation. This release phenomenon is the basis of certain operations which are described in brief.

Mass evacuation or defæcation proper is rendered necessary and possible because of the capacity of the colon for storing fæces until it becomes convenient to defæcate. Storage is apparently a function controlled by the pelvic nerves, and when these are divided, the peristaltic action of the gut is released from the controlling influence and small amounts of fæcal material are passed at frequent intervals. Defæcation proper depends on the integrity of the pelvic nerves and is lost when these are destroyed. The effect on the distal colon of stimulation of the pelvic nerves in dogs is described. Usually the result is similar to that described by Elliott and Barclay-Smith. The muscle of the longitudinal coat contracts almost at once, shortening the colon and drawing it down towards the pelvis. After an interval a contraction of the circular coat begins at the upper end of the distal colon and spreads downwards, driving fæces before it. Sometimes this is followed by other waves of like nature.

Certain clinical observations are recorded which seem to lend support to the conclusions drawn from experiments in animals. After complete severance of the nerves of the cauda equina, a man passed small amounts of fæcal matter at intervals throughout the day, apparently having lost the power to store fæces,

and the faculty of mass defæcation. After excision of the rectum, which results in the destruction of most of the colonic branches of the pelvic plexus, the remaining portion of the distal colon is deprived of its pelvic nerve-supply and that part of the lumbar sympathetic nerve-supply which passes through the pelvic plexus. Fæces are usually passed through a sigmoid colostomy several times daily, and at each voiding several small amounts are passed at short intervals, evidently by peristaltic action. It would appear that the capacity for storage is lost and that the inherent peristaltic mechanism of the bowel, released from the controlling influence of the pelvic nerves, takes charge and expels fæces as they become available.

A brief description of certain operations which have been advocated in the treatment of desperate constipation is given. In all of these the lumbar outflow of the sympathetic nervous system to the lower abdominal viscera is destroyed to a greater or less extent. The beneficial effect is probably due to the release of the colonic musculature from abnormal reflex influences of an inhibitory nature such as may be observed experimentally when a sensory nerve is stimulated, the spinal cord and sympathetic nerves being intact. That it is not due to the 'unopposed' action of the pelvic nerves is suggested by the fact that when the latter are destroyed, either in animals or man, constipation does not necessarily result, althought the lumbar sympathetic nerves remain intact.

REFERENCES

[1] HOLZKNECHT, G., "Die normale Peristaltik des Kolon", *Münch. med. Woch.*, 1909, lvi, 2401.

[2] LANGLEY, J. N., and MAGNUS, R., "Some Observations of the Movements of the Intestine before and after Degenerative Section of the Mesenteric Nerves", *Jour. of Physiol.*, 1905, xxxiii, 34.

[3] ELLIOTT, T. R., and BARCLAY-SMITH, E., "Antiperistalsis and other Muscular Activities of the Colon", *Ibid.*, 1904, xxxi, 272.

[4] LANGLEY, J. N., and ANDERSON, H. K., "On the Innervation of the Pelvic and Adjoining Viscera. Part I. The Lower Portion of the Intestine", *Ibid.*, 1895, xviii, 67.

[5] LANGLEY, J. N., and ANDERSON, H. K., *Ibid.*, 1896, xx, 372.

[6] TRUMBLE, H. C., "The Plan of the Visceral Nerves in the Lumbar and Sacral Outflows of the Autonomic Nervous System", *Brit. Jour. Surg.*, 1934, xxi, 664.

[7] BAYLISS, W. M., and STARLING, E. H., "The Movements and Innervation of the Small Intestine", *Jour. of Physiol.*, 1899, xxiv, 99.

[8] BAYLISS, W. M., and STARLING, E. H., "The Movements and Innervation of the Large Intestine", *Ibid.*, 1900, xxvi, 107.

[9] ELLIOTT, T. R., "The Innervation of the Bladder and Urethra", *Ibid.*, 1907, xxxv, 367.

[10] MERZBACHER, L., "Die Folgen der Durchschneidung der sensibeln Wurzeln in unteren Lumbalmarke, im Sacralmarke und in der Cauda equina des Hundes", *Arch. f. d. ges. Physiol.*, 1902, xcii, 585.

[11] BARRINGTON, F. J. F., "The Nervous Mechanism of Micturition", *Quart. Jour. Exper. Physiol.*, 1914–15, viii, 33.

[12] ROYLE, N. D., "A New Operative Procedure in the Treatment of Spastic Paralysis and its Experimental Basis", *Med. Jour. of Australia*, 1924, i, 70.

[13] WADE, R. B., "The Operative Treatment of Hirschsprung's Disease: a New Method with an Explanation of the Technique and the Results of Operation by N. D. Royle", *Ibid.*, 1927, i, 137.

[14] JUDD, E. S., and ADSON, A. W., "Lumbar Sympathetic Ganglionectomy and Ramisectomy for Congenital Idiopathic Dilatation of the Colon", *Ann. of Surg.*, 1928, lxxxvii, 479.

[15] TRUMBLE, H. C., "The Surgical Treatment of Constipation", *Med. Jour. of Australia*, 1931, ii, 405.

[16] RANKIN, F. W., and LEARMONTH, J. R., "Section of the Sympathetic Nerves of the Distal Part of the Colon and the Rectum in the Treatment of Hirschsprung's Disease and Certain Types of Constipation", *Ann. of Surg.*, 1930, xcii, 710.

SHORT NOTES OF RARE OR OBSCURE CASES

POST-TYPHOID CHONDRITIS WITH ABSCESS FORMATION

By R. C. BROCK

SURGICAL TUTOR AND REGISTRAR, GUY'S HOSPITAL

Post-typhoid infection of costal cartilage must be a rare condition since reference to the standard text-books of medicine, surgery, and pathology reveals that little or nothing is said about it. Those authors that do mention it amongst the many possible complications and sequelæ of typhoid fever merely state that it may occur. Post-typhoid infection of bone appears to be less rare and is more fully described. The following case merits recording not only as an instance of post-typhoid chondritis, but also because it demonstrates the morbid anatomy of infection of costal cartilage by *B. paratyphosus B.*

History.—J. S., aged 32, a medical practitioner, developed a painful swelling in the neighbourhood of the inner end of the clavicle in May, 1934. The condition was associated with pyrexia and there was considerable pain in the adjacent muscles and those of the shoulder. He was compelled to rest in bed, and after two weeks the pain stopped and the acute swelling subsided. Towards the end of August pain was again noticed and a small lump appeared just below the inner end of the left clavicle and slowly increased in size.

On Examination.—Examination revealed a smooth, almost painless, firm swelling situated very accurately over the first costal cartilage, to which it was attached. It could be ascertained with fair certainty that it did not arise in connection with sternum, rib, or clavicle. There were no other abnormal physical signs. X-ray examination of the bones of the neighbourhood and of the lungs was negative. In view of the apparent strict localization of the condition to the costal cartilage none of the suggested diagnoses of gumma, growth, or tubercle seemed likely. The acute onset with fever and pain was against them all. Tubercle, which was the most likely on the grounds of frequency, gives a soft fluctuating abscess and not a firm lump. The Wassermann reaction was negative. There remained the possibility of a post-typhoid infection as one of the few causes of the rare condition of costal chondritis.

Inquiry revealed the fact that in 1920 (fourteen years before) there had been an illness, suspected at the time to be paratyphoid fever, but unconfirmed as blood culture and the Widal reaction had both been negative. The Widal reaction was repeated and found to be positive to *B. paratyphosus B* in a dilution of 1–500. Muir and Ritchie, in their text-book of bacteriology, state that agglutination with a dilution of 1–25 is positive for *B. paratyphosus B.* The titre given was, therefore, very high. Examination of the stools and urine revealed no evidence that the patient was a carrier.

OPERATION.—Operation was performed in October, 1934, six months after the onset of symptoms. A slightly oblique incision was made over the first costal cartilage. The underlying pectoral muscle was found to be fibrous and indurated, and lying on the anterior surface of the first costal cartilage was a small abscess cavity with dense fibrous walls containing about 1 c.c. of thin yellow pus. On exposing the anterior surface of the cartilage more fully it was seen to be perforated in several places by small holes much as one sees in old worm-eaten furniture. (This appearance has been noticed before by the writer in the case of typhoid chondritis.) A probe could be passed into a definite abscess cavity in the interior of the cartilage, revealing that the condition was similar to a 'collar-stud' abscess. Having regard to the anatomy of the part and the dense fibrosis around, there was a great temptation to be content with a liberal curettage of the affected area. As such a course would almost inevitably lead to persistent sinus formation, the whole costal cartilage was excised from sternum to rib attachment. This is the only certain way to prevent a chronic sinus following infection of a costal cartilage. The cavity left was plugged with a small flap of the overlying pectoral muscle and the wound was closed without drainage. Apart from a slight serous discharge from one portion of the wound for some twenty-four hours, healing occurred by primary union. *Fig.* 181 shows the excised specimen. The irregular central abscess cavity and the 'worm-eaten' appearance given by the cloacæ in the cartilage which led to the more superficial abscess are well seen.

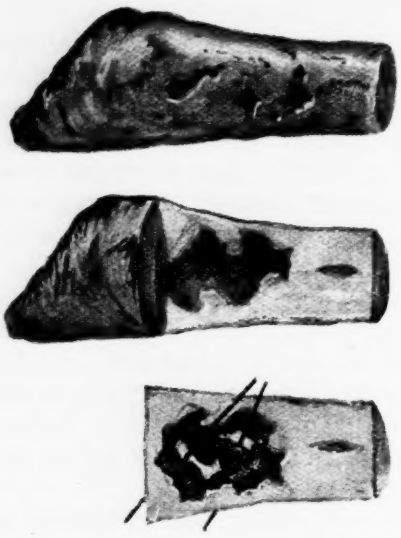


FIG. 181.—Costal cartilage excised at operation.

Culture of the pus from the cavity gave a pure growth of *B. paratyphosus B.* Muir and Ritchie state that the tendency to form abscesses from which the specific organism can be recovered is now recognized as a feature in the complications or sequelæ of infection with the *B. paratyphosus B.* In fact the organism was first isolated from such suppurative lesions.

SUBSEQUENT HISTORY.—During recent years the patient has been subject to attacks of lumbago and fibrositis. It will be interesting to see if these attacks disappear now that a definite focus of infection has been removed.

Commentary.—Points of interest in the case are :—

1. The diagnosis of a subacute inflammatory swelling over a costal cartilage as a post-typhoid abscess.

2. The complete excision of the infected area followed by rapid healing. The books state that a chronic sinus usually follows typhoid infection of bone or cartilage.

3. The morbid anatomy of the specimen removed.

4. The recovery of the organism in pure culture after a lapse of fourteen years.

AN ANOMALOUS DUODENAL POUCH

By J. C. BOILEAU GRANT
DEPARTMENT OF ANATOMY, UNIVERSITY OF TORONTO

THE anomalous bag or pouch of duodenal mucosa here depicted (*Figs.* 182, 183) was found in a male aged 47 years and was brought to my attention by a student (W. D.). It was about the size of the terminal phalanx of a finger, 25 mm. by 12 mm. It hung within the lumen of the gut like a hollow polypus whose mouth was directed towards the pylorus. It was attached by one lip of its slit-like mouth; the other lip was free, and on the margin of this free lip the common orifice of the bile and pancreatic ducts opened.

It is well known that the valvulæ conniventes in the region of the papilla of Vater have a characteristic arrangement; one forms a hood over the papilla, another descends from the papilla as a longitudinal fold, the plica longitudinalis duodeni. These could not be identified in this specimen. The interior of the pouch was smooth except for the presence of a longitudinal fold on its posterior wall.

FIG. 182.—A photograph of the pouch.

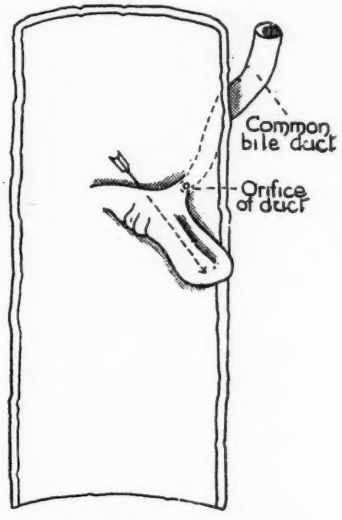


FIG. 183.—A sketch of the pouch.

Histological sections of the posterior wall of this pouch show that it consists of a reduplication of the entire mucous membrane of the gut—that is to say, the inner and outer surfaces are lined with villi which are supported by the usual reticular stroma, and in the middle, two layers of tunica muscularis mucosæ are applied to each other. No glands of Brunner are to be seen. That the tunica muscularis mucosæ is reduplicated is significant. Sections taken for comparison from adjacent parts of the duodenal wall make it clear that this point is not in question.

As to the cause of its formation, a variety of reasons will no doubt suggest themselves as possible. The actual cause, however, can only be surmised. It is more than probable that peristaltic action of the bowel had caused the pouch to increase in size. Had radiograms of an opaque meal been taken, the pocket would no doubt have filled and would have simulated a duodenal diverticulum. The site and outline of the pouch and the age of the patient would have tended to substantiate this suspicion.

That such a mass within the lumen of the gut might give rise to symptoms of ileus is evident. In fact, in the hospital record it is stated that the subject had had pain in the gall-bladder region for three years, that he was rarely free from pain for half a day at a time, and that he suffered from nausea and occasionally from vomiting after eating. The cause of death was septic bronchopneumonia.

A HUGE FIBRO-ADENOMA OF THE BREAST

By KENNETH MACKENZIE, Auckland, N.Z.

A woman, aged 34, said that for two years a tumour had been steadily growing in her left breast. She had gone for treatment to a religious revivalist and faith-healer and had been in his hands for many months. Three weeks ago ulceration had occurred and there had been a foul black discharge, the stench from which had driven her to seek medical advice. There had been no pain, but great incon-

Fig. 184.—Large fibro-adenoma of breast.

venience from the bulk and weight of the breast. Rapid deterioration in general health had taken place since the breaking-down had occurred.

Fig. 184 shows the condition that was present. There was no fixation of the mass to the chest wall, and removal was easy. Convalescence was uneventful, and two years later the woman was in excellent health.

The tumour weighed 35 lb. and was a fibro-adenoma.

SPONTANEOUS RUPTURE OF THE SPLEEN

By W. D. GALLOWAY,
ASSISTANT SURGEON, HUDDERSFIELD ROYAL INFIRMARY

Mrs. F. H., aged 29, whilst kneading bread at 10.45 a.m. on March 17, 1934, was suddenly seized with severe pain in the left hypochondriac region. The pain, which came in spasms, grew rapidly worse and was felt in the left shoulder. The patient stated that she had fainted. She had had no illnesses of any note, had not suffered from malaria, and no history of injury however slight could be elicited after the most exhaustive interrogation. The last menstrual period occurred on March 10, 1934. Her periods up to the time of her last pregnancy had been regular, 3/28 with a normal loss; since the birth of her last child, however, the menstrual ratio had been 7–8/28 and the loss excessive. The patient had two children, aged 3 years and 1 year respectively; both were born by natural forces, and the subsequent puerperia as far as could be ascertained were normal. No miscarriages, no intermenstrual discharge. The bowels were regular, micturition was normal, and the patient had not vomited.

Fig. 185.—Ruptured spleen.

On Admission.—The temperature was 99° and the pulse 112. The patient's lips were cyanosed and the mucous membranes pale. There was no restlessness or air-hunger. She complained continually of pain in the left shoulder, and it was observed that when she was rolled on to the right side in an attempt to elicit movable dullness pain was urgently complained of in the right shoulder, but when she was allowed to sink back again into the recumbent position the pain shifted with the altered position into the left shoulder again. This phenomenon of shifting pain in the shoulder was a marked feature of the case and was noticed and remarked on by all present. The abdomen moved well with respiration, was tumid and very tender, especially over the left hypochondrium; there was no rigidity.

Per vaginam—the uterus was firm, bulky, and freely movable; the fornices revealed no abnormality other than a marked tenderness in the pouch of Douglas.

DIAGNOSIS.—This was not made with certainty; perforation of a hollow viscus and rupture of an isthmial pregnancy were considered.

OPERATION.—The abdomen was opened by a left paramedian incision about 5 in. long, about four-fifths being situated above the level of the umbilicus. When the peritoneum was incised only omentum was visible, but on manipulating this about a pint of blood gushed into the wound. The pelvis was at once explored, and both uterus, tubes, and ovaries were found to be normal.

A hand passed into the left hypochondrium detected clots, and this in turn led to a careful examination of the spleen, which seemed unduly friable and appeared to have a small irregular laceration on its diaphragmatic surface (*Fig.* 185). The incision was slightly lengthened and the spleen removed. Most of the blood and clots were evacuated and the peritoneal cavity was left comparatively dry. A transfusion of one pint of blood was administered at the end of the operation.

Fig. 186 shows a microscopical section of the spleen.

FIG. 186.—Microscopical section of spleen.

SUBSEQUENT PROGRESS.—A small abscess in the abdominal wound was opened on the tenth day, after which the incision healed uneventfully. On April 9 the patient developed an attack of thrombosis in the left leg which lasted four weeks. She was discharged on May 24 at her own request. She was seen on Dec. 13 and still appeared rather anæmic. The abdominal wound had healed well and no sign of an incisional hernia could be detected. She still complained of some œdema in the left leg towards the end of the day.

Observations.—

1. The complete absence of nausea and vomiting was noteworthy.

2. Shoulder pain, especially pain moving from the uppermost shoulder to the shoulder on which the patient was recumbent when turned from the supine to a lateral position, was a marked feature of the case.

3. A perusal of the literature seems to show that these cases are seldom correctly diagnosed before abdominal section; but had the possibility of a spontaneous rupture of the spleen been entertained, this, together with the initial site of the pain and a consideration of the physical signs, should have suggested the correct diagnosis.

BIBLIOGRAPHY

SUSMAN, M. P., *Brit. Jour. Surg.*, 1927–8, xv, 47.
BAILEY, HAMILTON, *Ibid.*, 1930, xvii, 67.

SUPERNUMERARY CARPAL BONE

BY N. G. W. DAVIDSON, O.B.E.
VISITING SURGEON AND HONORARY LECTURER IN CLINICAL SURGERY, VICTORIA INFIRMARY, GLASGOW

IT is well recognized that supernumerary carpal bones do occur, and according to Köhler the most common is the os trapezoid secundarium. One, however, that

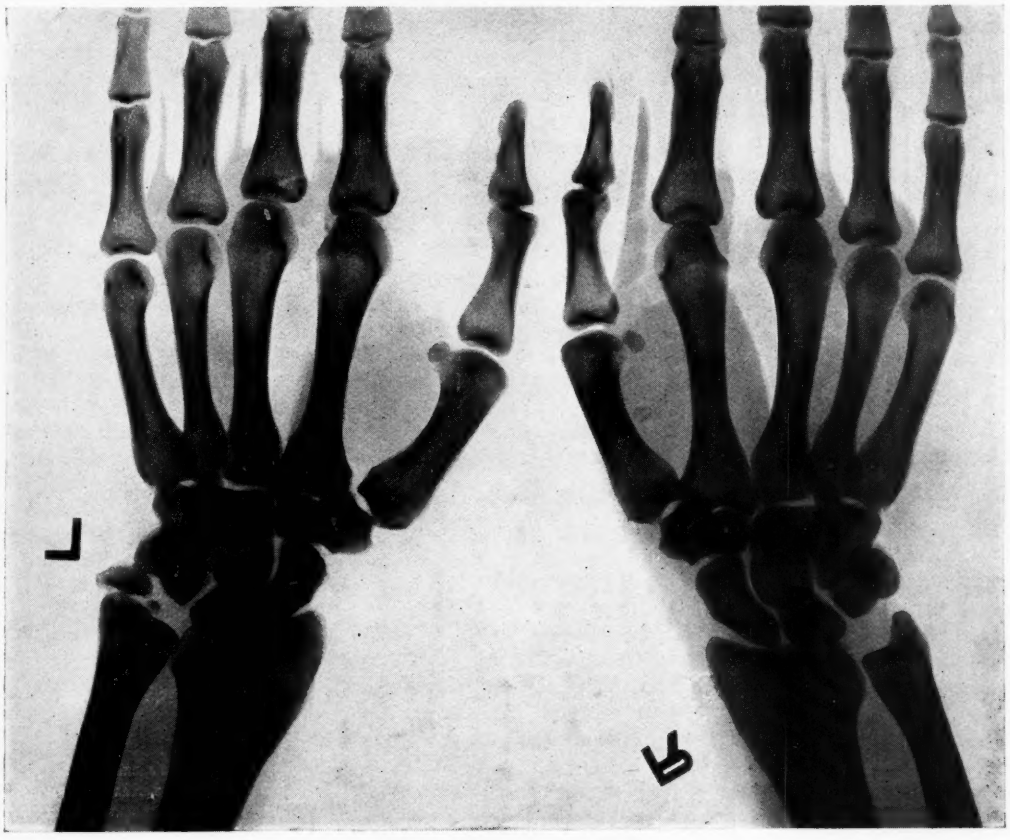


FIG. 187.—Supernumerary carpal bone.

is rarely met with is the os triangulare or the os intermedium antibrachii. It has been described as being a unilateral condition, and I have been unable to find an example of it occurring bilaterally. There is some doubt as to the origin of the

bone. In some cases where the styloid process of the ulna has been detached and become enlarged and ceases to look like a fragment it has been considered as the origin. Non-traumatic cases have occurred, or at least been described, but the most reasonable explanation for the formation of this bone seems to be that given by Pfitzner—that it is due to a broken-off pseudo-arthrotically healed process of the styloid.

The present case, P. R., aged 22, gave a history of an accident in January, 1935, the accident being a twist to his left wrist. He informed us that for more than twelve months he had been finding discomfort in his wrist in making certain movements, and when making them he felt a click. On further questioning he informed us that he had ' broken ' his wrist at the age of 16, and that the wrist had not felt right since then. Clinical examination revealed nothing that could be described as abnormal: no click could be elicited nor could the patient himself make the click voluntarily. An X-ray was taken, and a beautiful example of an os triangulare was seen (*Fig.* 187). It will be noted in the X-ray that the styloid process of the ulna has been broken off and that the typical triangular-shaped supernumerary carpal bone is well shown.

REVIEWS AND NOTICES OF BOOKS

St. Bartholomew's Hospital Reports. Edited by LORD HORDER OF ASHFORD, W. GIRLING BALL, RONALD G. CANTI, CHARLES F. HARRIS, WILFRED SHAW, H. H. WOOLLARD, R. C ELMSLIE, GEOFFREY EVANS, and J. PATERSON ROSS. Demy 8vo. Pp. 279 + xxiv. Illustrated. 1934. London: John Murray. 21s. net.

FOR the writer the 1934 volume of these reports has a note of personal sadness, for it contains a short obituary notice of William Foster Cross, whose colleague the reviewer was privileged to be at the Fishmongers Hall Hospital for Officers during the war. The biographer very happily summarizes Cross's chief characteristic as an anæsthetist when he says "that to be really appreciated as a man he had to be seen contending with a fractious surgeon and a difficult patient". Besides being a most competent anæsthetist, Cross was always obliging to those with whom he had to work, and his consideration and patience for nerve-shattered officers was extraordinary considering the claims he had on his time.

The problem of peptic ulcer is considered anatomically, pathologically, and surgically, in some very full and careful papers: we cannot find that the matter is advanced appreciably.

Professor Fraser, Sir Thomas Dunhill, and Dr. Spence similarly deal very thoroughly with the toxic goitre in its anatomical, physiological, and surgical aspects: this is a most comprehensive piece of work which brings the matter right up to date, and must be a most valuable guide to those who are interested in the treatment of patients suffering from this disease.

The Anatomy of Surgical Approaches. By L. C. KELLOGG, A.B., M.D., Professor of Anatomy, College of Medical Evangelists, Loma Linda and Los Angeles, California. Crown 8vo. Pp. 134 + x, with 29 illustrations. 1934. London. Baillière, Tindall & Cox. 7s. net.

THIS small volume appears to have been started with the idea of giving the surgeon an anatomical guide to certain operative procedures, but as the volume developed many details of surgical technique crept into the book and its original purpose has, therefore, been somewhat obscured. In our judgement, if it had been limited to the anatomy of surgical approaches it might have served a useful purpose, but it is scarcely possible to write even a superficial account of operative surgery within the scope of such a volume. It limits itself largely to the extremities and head and neck, dealing only with the nerves, arteries, and bones. The text is accurate, but a considerable amount of unnecessary elementary detail might be eliminated. The few line diagrams are helpful in making clearer what is described in the letterpress.

Surgical Applied Anatomy. By Sir FREDERICK TREVES, Bart., revised by C. C. CHOYCE, C.M.G., C.B.E., B.Sc., M.D., F.R.C.S., Professor of Surgery, University of London, etc. Ninth edition. F'cap. 8vo. Pp. 720, with 174 illustrations, including 66 in colour. 1934. London: Cassell & Co. Ltd. 14s. net.

To dip into a fresh edition of Treves' *Surgical Applied Anatomy* produces a feeling akin to the sorrow and regrets which are occasioned by visiting one's birthplace or preparatory school. Any new edition cannot be the same as our old friend, and therefore it is not so good. And where is the story which first aroused our interest in the viscus concerned? Gone! One feels one has lost an old friend, yet the vast store of anatomical detail remains: one can scarcely raise an anatomical question to which the answer cannot be found here. The new edition is well illustrated, is commendably accurate, and is nicely published. As the viewpoint of the surgeon has since Treves' day veered from the limbs to the abdomen, and more recently to the brain and thorax, so the space allotted to these different parts has gradually been amended; but in the present edition the autonomic nervous system is not described in accordance with present-day beliefs.

There is a puzzling mixture of nomenclature which in a future edition it is hoped will be eliminated by the substitution of the Anatomical Society's nomenclature for the two now in use.

Illustrations of Regional Anatomy. By E. B. JAMIESON, M.D., Senior Demonstrator and Lecturer, Anatomy Department, University, Edinburgh. F'cap. 4to. Published in five sections: Section I, Central Nervous System, 48 plates, 7s. 6d. Section II, Head and Neck, 61 plates, 10s. Section III, Abdomen, 37 plates, 5s. 6d. Section IV, Pelvis, 30 plates, 3s. 6d. Section V, Thorax, 27 plates, 4s. 1934. Edinburgh: E. & S. Livingstone. Complete set, 30s. net.

PROFESSOR JAMIESON'S atlas of coloured diagrams of human anatomy is a delightful production. It is said they are 'paraphrases' of the author's blackboard diagrams, which must indeed be things of beauty. The plates are fitted on to looseleaf pillars and, printed on only one side of the page, may be pasted in notebooks. The body is divided into regions and is dealt with in five sections which do not include the arm or leg: this is, in our judgement, to be regretted, but no doubt cost was the deciding factor. At 30s. it seems a marvellously cheap production. As a member of the Sub-committee of the Anatomical Society which, after much labour, produced the nomenclature, the author rightly makes use of it, adding the B.N.A. terms in brackets when the names are medically different.

Handbook of Anæsthetics. By J. STUART ROSS, M.B., Ch.B., F.R.C.S.E., late Lecturer in Practical Anæsthetics, University of Edinburgh; and H. P. FAIRLIE, M.D., Anæsthetist to the Western Infirmary, the Royal Hospital for Sick Children, and the Dental Hospital, Glasgow. Fourth edition. Crown 8vo. Pp. 299 + x, with 66 illustrations. 1935. Edinburgh: E. & S. Livingstone. 10s. 6d. net.

IN preparing the fourth edition of this popular little work on anæsthesia, Dr. Fairlie has shown excellent judgement in selecting what to discard and what to retain, and has brought his subject up to date, although cyclopropane and vinesthene have not been included, owing, probably, to these drugs being so recently introduced that the author found it difficult to express a practical view as to their properties. Valuable space has not been sacrificed to make room for unnecessary illustrations; the subject matter is put clearly and with enough detail to make the description of methods and apparatus easy to understand. The section dealing with physiology has been carefully revised and gives us a useful summary of the most recent teaching with reference to surgical shock, and in this connection the reader is warned of the old fallacy of regarding deep ether anæsthesia as a safeguard. It is perhaps rather surprising that for ordinary work nitrous oxide and oxygen anæsthesia has not been given greater prominence. We feel that this edition well maintains the good tradition of its predecessors as an essentially practical and very valuable book for all interested in this somewhat complex subject. The publishers are to be congratulated upon the excellent manner in which it has been turned out.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest for our readers.]

A Text-book of Surgery for Dental Students. By G. PERCIVAL MILLS, M.B., B.S. (Lond.), F.R.C.S., Hon. Surgeon, General Hospital, Birmingham, etc.; and HUMPHREY HUMPHREYS, O.B.E., M.C., T.D., K.H.P., M.B., Ch.B., M.D.S. (Birm.), L.D.S. (Eng.), Lecturer on Dental Anatomy, Birmingham University, etc. Fourth edition. Large 8vo. Pp. 342 + xii, with 63 illustrations. 1935. London: Edward Arnold & Co. 14s. net.

The Diseases of the Endocrine Glands. By HERMANN ZONDEK, M.D. (Berlin), translated by CARL PRAUSNITZ, M.D. (Breslau), M.R.C.S., L.R.C.P., Hon. Research Fellow, Victoria University of Manchester. Large 8vo. Pp. 492 + xi, with 168 illustrations. 1935. London: Edward Arnold & Co. 40s. net.

The Principles and Practice of Urology. By FRANK HINMAN, A.B. Leland Stanford Junior University, M.D. Johns Hopkins Medical School; Clinical Professor of Urology at the University of California Medical School. Large 8vo. Pp. 1111, with 513 illustrations. 1935. London and Philadelphia: W. B. Saunders Company. 45s. net.

Surgical Nursing and After-treatment. A Handbook for Nurses and Others. By H. C. RUTHERFORD DARLING, M.D., M.S. (Lond.), F.R.C.S. (Eng.), F.R.F.P.S. (Glasgow), Surgeon, Prince Henry Hospital, New South Wales Hospital (Langton Clinic), etc. Crown 8vo. Pp. 738 + xii, with 187 illustrations. 1935. London: J. & A. Churchill Ltd. 9s. net.